Author’s response to reviews

Title: Analysis of Risk Factors for Cervical Lymph Node Metastasis of Papillary Thyroid Microcarcinoma: A Study of 268 Patients

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Author’s response to reviews:

Dear Dr. Sawicka-Gutaj:

I am writing to submit a revised version of our manuscript, entitled “Analysis of Risk Factors for Cervical Lymph Node Metastasis of Papillary Thyroid Microcarcinoma: A Study of 268 Patients” (MS ID: BEND-D-19-00208).

Per reviewer comment, we re-analyzed the association between cervical LN metastasis and tumor diameter based on pre-op ultrasound data instead of pathologic examination. The analysis confirmed increased risk of cervical LN metastasis with larger tumor diameter (OR=3.172 for >5mm).

With regards to analysis in patients with cN0, we reviewed all 268 cases but identified only 4 cases in which ultrasound report clearly reported cN1 despite of the fact that 70 out of the 268 patients had pN1 to central lymph nodes. In other words, most cases included in the current studies had cN0 status. The low rate of metastasis to the cervical lymph nodes (vs. reported in other studies) most likely reflects the much smaller tumor diameter in the current study (≤10 mm on pathologic examination).
During the revision, I collaborated with a professional medical editor to revise the entire manuscript, with particular emphasis on abbreviation use (to eliminate ambiguity).

I thank you for giving us an opportunity to revise this manuscript, and look forward to hearing from you.

Yours,
Fei Wang

Point-to-point responses

Reviewer #1

Question/comment #1:
The manuscript presented by Jian-hua Gu et al. deals with an important issue of the risk factors for the cervical lymph node metastases in papillary thyroid microcarcinoma (PTMC). In clinical practice, this malignancy is considered quite indolent, with an excellent long-term prognosis. Therefore, therapeutic measures tend to be limited to thyroid surgery without subsequent radioiodine ablative treatment. However, a small proportion of the PTMCs actually give rise to the metastatic lesions in the cervical lymph nodes. At present, cases with increased metastatic potential are difficult to distinguish based on routine histopathology evaluation of the thyroid tumour. Hence investigation of the risk factors for the cervical lymph node metastases seems a valuable initiative, which could provide precious therapeutic guidance in PTMC patients.
The study comprised data collected from 268 patients with PTMC, with complete clinical description and histopathology results. This is an elegant retrospective analysis, which clearly demonstrates that male gender and thyroid tumour size are independent risk factors for the cervical lymph node metastases in PTMC. According to the current analysis, up to one third of the PTMC patients present with cervical lymph node metastases Therefore, male patients and those with larger microcarcinoma (still less than 1 cm of diameter) need to be monitored more closely. Moreover, the data obtained in this study support routine central lymph node dissection during thyroid surgery, as preoperative ultrasound and cytology evaluation may not detect minute metastases. Overall, the analysis presented in the manuscript, although retrospective and not very innovative, adds up to the former knowledge on prognostic factors in PTMC. On the contrary, the investigation of skip metastases, even if quite detailed, comprises just four individuals. This is a major limitation, which precludes from drawing any meaningful conclusions, and therefore this analysis might be omitted in the manuscript.

Author response:
Per reviewer suggestion, I refrained from analyzing skip metastasis in the revised manuscript.

Question/comment #2:
Table 1 with patient demographic characteristics apparently lacks number and proportion of cases with capsular invasion and extrathyroidal extension.

Author response:
I apologize for the negligence in the original manuscript. Number and proportion of the cases with capsular invasion and extrathyroidal extension are now added to Table 1 in the revised manuscript.

Reviewer #2

Minor comment #1
Table 1: results for capsular invasion and extrathyroidal extension? (I suggest that "capsular invasion" should be deleted); How many lateral lymph node dissection (LND) were performed?

Author response
I apologize for the negligence of not having actual data for capsular invasion and extrathyroidal extension in Table 1. Number and percentage of patients having these features are now added to the manuscript following the comment of the first reviewer. Lateral lymph nodes were dissected in 9 out of 268 patients (4 to only lateral lymph nodes and 5 to both central and lateral lymph nodes); pathologic examination revealed metastasis in all 9 patients.

Minor comment #2
Figure 1: "PTC" is probably PTMC; How can you exclude 78 non-PTMC among a group of 346 PTMC? Too many patients were excluded from the study, and the rate of incomplete data is very high.

Author response
"PTC" in the fourth insert on the left side (n=429) stands for “papillary thyroid cancer”, and was correct. “PTMC” in the fifth insert no the left side (n=346) and in the fourth insert on the right side (n=83) was wrong, and has been replaced with “PTC”. Only the last insert on the left side (n=268) refers to PTMC. I apologize for confusing the reviewer with incorrect abbreviations, and corrected such mistakes. Corresponding description in the main text was also carefully revised. I agree with the reviewer that the high rate of incomplete data is an important caveat in the current study, and discussed this issue as a limitation in the current study.

Major comment #1
The sample size was quite small (268 patients).

Author response
Papillary thyroid microcarcinoma is typically managed using a “wait-and-watch” strategy. From this perspective, 268 cases with complete postop pathologic data are valuable. I agree with the reviewer that 268 patients are not ideal to attempt a multivariate regression analysis to determine the full spectrum of risk factors for cervical lymph node metastasis. Nonetheless, we clearly identified male sex and larger tumor diameter (&gt;5 mm on pre-op ultrasound) as the risk factors, and believe that such findings are clinically relevant. We are currently collecting more cases together with a few other centers under a prospectively designed protocol.

Major comment #2
You had only 83 PTMC with multifocality, and 268 solitary PTMC. The rate of multifocality is usually higher. Could you explain?

Author response
“83” is the number of PTC with multifocality, regardless of tumor size, but was mistakenly spelled as “PTMC” in the original manuscript. I apologize for misleading the reviewer. In the current study, PTC with multifocality was excluded during case selection for PTMC cases. Indeed, multifocal PTC is not considered microcarcinoma regardless of lesion size.

Major comment #3
Definition of the studied population is not clear. "CLNM" means sometimes "cervical" LNM, and sometimes "central" LNM (page 9, line 7; or Table 1).

Author response
I apologize for confusing the reviewer and limited the use of abbreviations to enhance clarity. In the revised manuscript, only “lymph node” is abbreviated. “cervical lymph node” now appears as “cervical LN”; “central lymph node” appears as “central LN”; “central lymph node metastasis” appears as “central LN metastasis”, “lateral lymph node metastasis” appears as “lateral LN metastasis”.

Major comment #4
How many patients were N1? 79 "cervical" or 88 (79 "central" + 9 "lateral")?

Author response
A total of 79 subjects had cervical lymph node metastasis: 70 to only central lymph nodes, 4 to only lateral lymph nodes and the remaining 5 to both central and lateral lymph nodes. In the revised Table 1, “LCLNM” is replaced with “lateral LN metastasis” to avoid potential misinterpretation; “CLNM” is replaced with “central LN metastasis”.

Major comment #5
What was the extent of thyroid resection: total thyroidectomy for all patients, or some patients had a lobectomy (the current recommended surgical procedure for microcarcinoma in most guidelines)?

Author response
All subjects received lobectomy. This has been clarified in the Methods section of the revised manuscript.

Major comment #6
What were your indications for LND? If I understand well, you performed prophylactic central LND, and lateral LND only in case of "suspicious" LNM (page 8, line 47), where were the suspicious LNM, in the central and/or the lateral compartments?

Author response
Central lymph nodes were dissected in all patients. Lateral lymph nodes were dissected only in patients with biopsy-proven metastasis to lateral lymph nodes.
Major comment #7
What is the proportion of patients with obvious N1 (therapeutic LND) among your patients? Your demonstration about the relationship between tumor size and the risk of N1 could especially be interesting in clinically N0 patients. Do you have this result?

Author response
We reviewed pre-op ultrasound in all 268 cases. cN1 to the lateral lymph nodes was reported in 9 cases; cN1 to the central lymph nodes was reported by ultrasound in only 4 cases, whereas post-op pathologic examination revealed metastasis to central lymph nodes in 75 cases (70 to only central lymph nodes and 5 to both central and lateral lymph nodes). In other words, majority of the patients included in the analysis had cN0 status.

Major comment #8
Did you exclude from the study PTMC diagnosed in the resected specimen (occult PTMC), that are very frequent? I understand that yes, since all your patients had a preoperative diagnosis of malignancy (positive cytology) (page 7, line 28). Could you give us the number of patients with occult PTMC who had surgery during the same period (and who were excluded from the study)? However, the range for maximum diameter of tumors included 1 mm. How is it possible to diagnose before surgery a PTMC of 1 mm in diameter? Please, explain.

Author response
We indeed excluded occult PTMC from data analysis. We encountered only 3 cases of occult PTMC during the past 2 years, but feel uncomfortable addressing this issue since most thyroid nodules considered benign based on pre-op assessment were treated with microwave ablation. The maximum tumor diameter in the original manuscript was based on pathologic examination, and thus included 1 mm. I agree with the reviewer comment that pre-op variables are of greater clinically relevance in assessing the risk of cervical LN metastasis, I re-analyzed the data using tumor diameter based on pre-op ultrasound examination. The analysis confirmed larger tumor diameter (>5mm on pre-op ultrasound) as a risk for cervical LN metastasis. The manuscript has been revised accordingly.