Peer Review File

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**Responses to Reviewer #1**

This review paper well summarized the current practices of clinical management of thyroid nodules and thyroid FNA cytology in Thailand comparing with practices of other countries.

**Response**: *We greatly appreciate a favorable evaluation of our manuscript by the reviewer.*

**Comment 1:** Page 10, In the "Well Differentiated Neoplasm of Uncertain Malignant Potential (WDT-UMP)", "neoplasm" should be changed into "tumor".

**Response:** *Thank you for pointing out this error. We have changed the word "neoplasm" to "tumor" as suggested.*

**Comment 2:** Tables 3 and 4 show all raw data. But it may be difficult to see whether there is a relationship or difference among variables just by looking at the raw data, but with forest plots of meta-analysis, any patterns that exist in the data become much easier to see.

**Response:** *We acknowledge the reviewer for this suggestion and have rearranged the data to a chart with range for comparison between all Thai series and a new table for comparison between the Thai series and the data from other meta-analyses.*

**Comment 3:** The English quality and grammar of the text is uneven, the manuscript should benefit from language editing.

**Response:** *Thank you for pointing this out. The manuscript has been submitted to office of research affairs, Chulalongkorn University, for professional proofreading by a native English speaker as mentioned in the acknowledgement.*

**Responses to Reviewer #2**

This study aimed to provide a local perspective on a broad topic concerning the management of thyroid nodules in Thailand. The authors commented on various aspects of thyroid nodules with a strong deviation to the pathology side. The information presented is a kind of unique and rare to approach online for an international audience. This makes a strong point of the manuscript. At the same time, there is a range of issues, from major to minor, which require significant amendments to improve the quality of the manuscript.

**Response**: *We sincerely thank the reviewer for giving a constructive criticism and valuable comments on our manuscript.*

MAJOR

1. Data curation

**Comment 1:** Data shown in Tables 3-4 are largely reproduced from Keelawat, 2017 (PMID

29161789), including 2 datasets from Chiang Mai (2011-2015) and Khon Kaen (2011-2015); both of which were somehow specified as "unpublished," which is counterintuitive.
**Response**: *We have re-arranged the data from tables 3-4 to a chart with range and a new table and removed the word "unpublished".*

**Comment 2:** One recent large-scale study has been ignored (J Med Assoc Thai 2018; 101:122); this should be added in the pooled results.
**Response:** *Thank you for the suggestion. We have added this series into the pooled results.*

**Comment 3:** It is strongly recommended to exclude considerably biased pre-Bethesda data (before 2010) from the pooled statistics of ROM and frequency of the diagnostic categories in Table 4 and Table 3, respectively.
**Response:** *We thank the reviewer for raising this issue. The pre-Bethesda data have been excluded from the pooled results as recommended.*

**Comment 4:** How many hospitals participated in the survey?
**Response:** *There were 51 hospitals from 5 regions participating in this survey. This number together with the demographic data of the respondents are demonstrated in table 1. We also added this information on p.3 under "Introduction"*

2. Abstract and Conclusion should be rewritten
**Comment 5:** These two key parts of the manuscript are not informative, currently containing repetitive, irrelevant, and in some sense, meaningless information, which is not logically bridged to the review itself. No reader is able to get a clue about management of thyroid nodules in Thailand after reading the abstract. Instructions for authors allow up to 450 words to be included in abstract and this space can and should be efficiently used. This critique is also applicable to the conclusion in its current form.
**Response:** *The abstract and conclusion have been re-written with an attempt to bridge them to the main content of the review as advised.*

3. Extensive (professional) language editing is mandatory
**Comment 6:** The manuscript is full of unnecessary vulgarisms, which is not compatible with a high-level international publication; some are listed among Minor comments below.
**Response:** *Thank you for the suggestion. The manuscript has been submitted to office of research affairs, Chulalongkorn University, for professional proofreading by a native English speaker as mentioned in the acknowledgement.*

**Comment 7:** Multiple typos and grammar issues: "book of the national guidelines" (p.3), "vocal fold" (p.4, instead of vocal cord), "two battery of tests" (p.5), "Royal College of Pathologist of Thailand" (p.9, should be Pathologists), "Well Differentiated Neoplasm of Uncertain Malignant

Potential" (p.10, should be Tumor), "Rossi" (p.15, should be Rosai), and many more.
**Response:** *Thank you for pointing these out. We have corrected all errors in the manuscript.*

**Comment 8:** Abbreviations are largely introduced but several of them were never used (should be used at least 3 times, as per conventional writing guidelines).
**Response:** *This issue has been fixed as advised.*

MINOR
**Comment 9:** The major focus in the review was made on pathology practice, while clinical aspects served as background information. Pathology is an important but relatively minor part of the thyroid care team. This should be correctly specified in the title and abstract, otherwise readers remain confused thinking that this review is dealing with a full spectrum of issues re. care of thyroid nodules (from reference levels of thyroid hormones to targeted therapy for advanced thyroid cancer).
**Response:** *Agree. And to emphasize the importance of pathology, we renamed the title to "Pathological Practice and Management of Thyroid nodules: A Thai Perspective"*

**Comment 10:** The authors repetitively claimed that "context of medical practice in our setting" is different from the rest of the world (p.2, p.3), however there is no clear explanation what difference has been meant.
**Response:** *Our setting is different from other places (esp. the western countries) in regard to ratio of pathologists and healthcare reimbursement system which were added on p.3 under "Introduction".*

**Comment 11:** It is said on p.3 that NCCN recommendations are most widely followed, while p.4 refers to ATA guidelines; which one is correct?
**Response:** *We would like to clarify that the national guidelines developed by NCI used NCCN as the main reference. Anyway, in real practice, ATA was the most popular guidelines among physicians.*

**Comment 12:** Page 5: "Free T3, free T4 and TSH are readily available... Other tumor markers..." T3, T4, and TSH are not tumor markers
**Response:** *Thank you for pointing out this error. We have replaced "Other tumor markers…." to "Thyroid tumor markers….".*

**Comment 13:** Please specify clearly what cytology reporting system, if any, is endorsed by the local guidelines?

**Response:** *The national guidelines endorse TBSRTC for cytological report. This was mentioned in*

*the last paragraph under the heading of "National guidelines for management of thyroid nodules in Thailand").*

**Comment 14:** P.7: "Molecular or immunocytochemistry are not included"; molecular what?
**Response:** *Sorry for such error. We have added "Molecular studies……" into this sentence.*

**Comment 15:** Thailand is well known as one of the world centers of TOETVA, which is completely ignored in the review.
**Response:** *Thank you for raising this issue. We have mentioned about this approach and add the references.*

**Comment 16:** P.8: reference to CAP Thyroid protocol is missing.
**Response:** *The reference to CAP Thyroid protocol has been added (p.9).*

**Comment 17:** What is an existing grossing protocol, especially for solitary encapsulated nodules? 10. P.10: "In most cases, these new terminologies [FTUMP] are not mentioned in the cytology reports" How come FTUMP can be diagnosed, suspected, or even mentioned in cytology report?
**Response:** *The details of grossing protocol has been added (reference 16). Regarding FTUMP, the whole sentence has been removed from the manuscript.*

**Comment 18:** P.10: "Thailand is well-known for its high quality treatment and successful..."; this statement is quite controversial. Please provide some good quality references to prove such a claim.
**Response:** *To provide an evidence to this statement, we have added a sentence "In 2010, the WHO examined and reported Thailand as one of the top 50 healthcare systems in the world and the second-best in Southeast Asia" and its reference (#21) to the manuscript.*

**Comment 19:** P.12: "For example, the Thai pathologists' day is held on May 26 which is the date when the late Prof. Chaloem Prommas, the first Thai pathologist, passed away on May 26, 1975. In 2017, the Royal College of Pathologists organized a charity run to increase the public's awareness of the pathology field." This reviewer would like to remind that the title of this manuscript is "Management of Thyroid Nodules: A Thai Perspective." Shall we expect that a broad audience attracted by this title, including endocrinologists, endocrine surgeons, radiologists, and other clinical specialists would be interested to learn about "charity run" and "Thai pathologists' day"?
**Response:** *We agree with the reviewer that these information are out of scope of this review and have removed them from the manuscript.*

**Comment 20:** P. 15: reference to CAP protocol is outdated, the current version is of 2019.

**Response:** *Thank you for pointing this out. We have edited it to the current version (reference #3).*

**Comment 21:** Table 3: why totals are placed on the top of the table?
**Response:** *We have re-arranged the data to a chart with range (figure 2).*

**Comment 22:** There are several meta-analysis papers used for comparison in Table 4, while only one study of Sheffield, 2014 chosen for Table 3. Why so?
**Response:** *Because table 3 represented the proportion of each Bethesda category which was available only in the study of Sheffield but not presented in other references. We have re-arranged the data to a bar chart with range (figure 2) and a new table (table 3) which have fixed this issue.*

**Comment 23:** What is logic of sorting studies top to bottom in Tables 3-4? Should be uniformly ordered either by year (descending or ascending) or alphabetically.
**Response:** *We have re-arranged the data to a chart with range (figure 2) and a new table (table 3) which have fixed this issue.*

**Comment 24:** The authors used several outdated meta-analysis papers as their reference numbers in Table 4. Please consider the paper of Vuong, 2020 (PMID 31883438), which is the most recent summary relevant to the Asian experience.
**Response:** *Thank you for the suggestion. We have added the paper of Vuong et al. (reference # 16) into our pooled results as recommended.*