Peer Review File

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Title: Implementing of ultrasound-guided fine-needle aspiration biopsy in thyroid surgery, a 6-year interrupted time series analysis in Qilu Hospital of Shandong University

Reviewer #1

This is a well-structured manuscript with proper statistical analysis. I have entered suggested English language modifications.

Author Answer: I appreciate your wonderful modification very much.

Reviewer #2

Thyroid fine-needle aspiration (FNA) cytology is a well-known minimally invasive diagnostic test for thyroid nodules, and it is used worldwide to triage patients for surgery and, at the same time, to reduce unnecessary diagnostic surgeries to benign thyroid lesions. However, actual impacts by FNA cytology on risks of malignancy of cytological categories were not well documented and analyzed in the modern era. This study provided a detailed analysis of what happened by the implementation of ultrasound-guided FNA (US-FNA) to the thyroid practice in a large academic center of the Chinese population.

Major criticism:

Comment 1: As some data in this thyroid practice were significantly different from those reported by thyroid practice in other countries, please provide background data of thyroid nodule practice in this Chinese population. They were 1) the total number of patients with thyroid nodules who underwent US examination, 2) indication of FNA (please cite any clinical guidelines if any) and proportion of FNA tests in patients with a thyroid nodule, and 3) how to triage patient for surgery using FNA (please cite any clinical guidelines if any).

Answer:

I modified the manuscript in the Material and Methods part and the Results parts using word tracking mode.

Comment 2: Please provide some more details (or any examples) as to how your thyroid FNA practice improved with experience, in addition to increased ROMs.

Answer:

This should be a different topic from the current study, therefore, we will discuss this in another manuscript. The current manuscript focuses on an interrupted time series analysis on the effect of implanting US-FNAB on thyroid surgery only.

The UG-FNAB in Qilu Hospital was operated by a technician and an endocrinologist in the endocrine clinic. The most common problem in the early phase of our FNA was high proportion of non-diagnostic samples due to unskilled operation, including poorly prepared, poorly stained, significantly obscured follicular cells and air-dry artifact.

For non-diagnostic and benign diagnostic category that discordance with the sonographic features, no-charge repeat FNAB is recommended for the patient to as modified in the manuscript. There is only one technician for UG-FNA, her operation improved gradually.

Comment 3: What were pitfalls in the early phase of UG-FNA practice, and how were they solved, if any?

Answer:

Yes, there are some pitfalls as described above. The most common one was air-drying effect and extensive obscuring blood hinders the evaluation of the follicular cells. Immediate fixation in ethanol is necessary for hematoxylin-eosin staining, and it was improved after constant practice.

Comment 4: This reviewer recommends showing the proportions of each cytological category and compare the incidence of the indeterminate category (combined AUS and FN) between the early phase and late implementation of UG-FNA. If the proportion decreased in the later phase significantly, please emphasize that the proportion of indeterminate nodules can be minimized with experience.

Answer:

Thanks for your great idea.

I totally agree your comment that the proportions of each cytological category could be improved with gradually increased practice. However, it is a great pity that there are different pathologists who do cytological diagnosis each year. I compared the proportion of each category in the years as shown in Table 1 below, the proportion of indeterminate nodules was much higher in 2018 (Liu Z. was in America for one year). It is because there were different pathologists who were on duty of thyroid FNA. There should be interobserver variation among the cytopathologists.

Follow-up and repeat FNAB are recommended for indeterminate category, and surgery is recommended for Suspicious of Malignancy and Malignancy group according to ATA guidelines. Therefore, although the proportion of this category is much higher in 2018, it has less impact on the treatment strategy of the patient underwent surgery, and as well as the Risk of Malignancy in surgically resected thyroid cases. In other words, the implementation of US-FNAB (the technology itself) could improve overall ROMs in surgically resected cases, and the indeterminate category has less impact on this effect.

Above all. I prefer that your recommendation should be discussed in another paper as a control study. The current manuscript mainly focused on the effect of implanting thyroid US-FNA as a pre-surgical diagnostic method, and it is an interrupted time series analysis comparing the two periods pre- and post- thyroid FNA, but not detailed practice in FNA period.

Table 1: The proportion of each diagnostic category according to the Bethesda System for Reporting Thyroid Cytopathology in Qilu Hospital of Shandong University.

Diagnostic Category	Proportion of each category			
	2015	2016	2017	2018
Bethesda I	3.0	4.0	5.9	1.8
Bethesda II	48.0	41.9	28.1	21.0
Bethesda III	4.7	8.6	9.5	17.5
Bethesda IV	0.1	0.3	2.3	4.8
Bethesda V	15.4	13.1	6.6	11.2
Bethesda VI	28.7	32.1	47.7	43.7

Minor criticism:

Comment 5: In Western thyroid practice, how to minimize missing malignancy is emphasized. If any, please mention any missing malignancy in this practice of a large number of patients. Are there any patients who developed distant metastasis after benign FNA results? If not, please state briefly that no missing malignancy nor malpractice litigation during the study period, between 2013 and 2018.

Already modified according to your comments.

Comment 6: On page 4: Do you mean by "An experienced fixed technician and endocrinologist performed UG-FNAB," that only one technician and only one endocrinologist carried out all (more than 10000) FNAs throughout the study period (from 2015 to 2018)? Do you mean one technician and one endocrinologist perform FNAs as a team, and several teams apply FNA to patients with thyroid nodules?

Yes, there was only one fixed technician for the FNA operation, and one of the ten endocrinologists who perform sonographic examination together with her.

Comment 7: The word "government" in the following sentence, "This is beneficial to avoid the physical injury caused by surgery and to reduce the financial burden of patients and the government." on page 11, better be replaced with the "health care system."

Thanks. Already modified.

Comment 8: English language editing is recommended for readers' better understanding.

Reviewer #1 kindly did English language editing for the whole manuscript. I accepted most of the modification before my editing.