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Response letter

In accordance to the reviewer 505453 suggestions, these corrections have been made (all of these coorections have been highlighted with yellow color in the revised manuscript):

Title Page

Please accept the addition of one more author Dr. Niki Margari, cytologist, at the second place, who helped substantially in writing the manuscript.

Abstract

1)"However several cases"
we deleted the word several

2)"In conclusion, patients who require repeated FNAs for indeterminate diagnoses will eventually require surgery given that the rate of malignancy is almost 20%."

We transformed the sentence to: In conclusion, patients who require repeated FNAs for indeterminate diagnoses will be resolved by repeat FNA in a percentage of 72-80%.

Introduction

1)"In this review we analyze all current literature regarding Thyroid Cytopathology"
We deleted the word all

Suspicious for Medullary Carcinoma

"There is a monomorphic population"
We added the following sentence: however, a significant number of aspirates can be pleomorphic., based on ref. 37

Anaplastic Carcinoma

The aspirates are described as showing "extreme celluarity".
We added the following text: They can be sparsely cellular, due to the marked fibrosis and hyalinization seen in some cases[20,53]. They can be readily classified as malignant due to nuclear pleomorphism, chromatin clumping, necrosis, atypical mitoses and other malignant features[41. We also added reference 53, which are being referred to this text.

Molecular

1)"The rate of malignancy in FNA-BRAF positive nodules has been shown to be 99.8%.[56]"
We added the following text: BRAF testing has been coupled successfully with the Bethesda Thyroid FNA classification system to offer molecular quality assurance on positive samples, as well as a diagnostic upgrade on samples of indeterminate diagnostic categories, such as AUS/FLUS and SFN/SHN[56]. The rate of malignancy in FNA-BRAF positive nodules has been shown to be 99.8%[57].

2)"BRAF is very helpful in FNA samples with indeterminate findings, such as the "suspicious for papillary carcinoma" ones.[55] "
We deleted that sentence and added the following text: It is a point of great significance that Ohori et al found a greater percentage of BRAF-mutated (V600E, K601E, and others) cases in the AUS/FLUS and SFN/SFN categories, rendering BRAF mutational testing a useful predictor of PTC diagnosis in these indeterminate cases[58]. While the V600E and K601E mutations were almost equally observed in the AUS/FLUS category, there were a slight predominance of K601E mutation in SFN/SHN category. In these SFN/SFN and AUS/FLUS cases with the K601E mutation, the cytomorphology of the PTC was impeded a more definitive diagnosis, on contrary to cases where the V600E mutation were observed, where the diagnosis resolved to a CL, TCV, or a solid diagnosis. The high sensitivity rate, as well as the high negative prognostic value of BRAF testing in AUS/FLUS and SFN/SFN categories have been also demonstrated by Alexander et al[59]. We also added references 58 and 59, which are being referred to this text.

3)"The above panel correctly identified cancer in 78.2%, whereas cytology identified 58.9% of the thyroid cancers."
We added the following text: Mose et al also examined the clinical utility of the above panel in thyroid FNA biopsies. When this panel was used for specimens with indeterminate cytology, sensitivity was 27%, specificity was 95%, PPV was 66%, and NPV was 78%[62]. In addition, Ohori et al investigated the utility of the above panel in specimens classified as FLUS. The molecular testing proved to have a high specificity, although the sensitivity was quite low (60%). Despite the fact that not all PTC were detected by this panel, a positive molecular test helped to refine the FLUS

cases into high-risk and low-risk categories[63]. We also added references 62 and 63, which are being referred to this text.

4)"It also predicted ml cancer in the majority of indeterminate samples, as well as of the"
We deleted the "ml"

Conclusion

"This system allows patients with FNAs showing focal atypia to undergo repeat aspiration prior to surgery. However, patients with repeated AUS/FLUS diagnoses will eventually require surgery given that the rate of malignancy is almost 20%.[9] "

We transformed the above statement to this: Therefore, in the majority of patients in the AUS/FLUS category (72-80%) the diagnosis will be resolved by repeat FNA, although 20-28% of them will have AUS/FLUS on the repeat aspirate and thus require surgery.

Figures

-We replaced Figure 3 with one with better magnification to adequately appreciate the Hurthle cells.
-We added Figure 4, a suspicious for thyroid carcinoma case.
-We also replaced Figure 2, with one of better quality.

<u>In accordance to the editor's suggestions, these corrections have been made (all of these coorections have been highlighted with cyan color in the revised manuscript):</u>

1) We wrote the journal name
2) We added a running title
3) We fulfilled authors' addresses
4) We wrote the affiliation of each author separately
5) We fulfilled the authors contribution sector
6) We declared no conflicts of interest
7) We corrected correspondent author's title, affiliation, address
8) We corrected the telephone number (there is no telefax number available)

9) We provided copyright statement
10) We wrote and recorded a core tip for this manuscript
11) We wrote a preferred citation for the manuscript
12) We reformatted all reference numbers like the guidelines
13) We provided DOIs and PMIDs for references which DOIs and PMIDs were available and we reformatted the references section like the guidelines