



**ARISTOTLE UNIVERSITY OF THESSALONIKI, SCHOOL OF MEDICINE**  
**SECOND SURGICAL PROPEDEUTIC DEPARTMENT**  
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**Editorial Bord ID: 00058511**

Thessaloniki 1 February 2023

Dr. Lian-Sheng Ma, Founder and Chief Executive Officer  
Baishideng Publishing Group, Inc.

Dear Editor:

Thank you for your preliminary decision regarding our invited paper entitled "Update on the current management of persistent and recurrent primary hyperparathyroidism after parathyroidectomy" (Manuscript NO: 83349), which was sent to the *World Journal of Clinical Cases* for publication as a *MiniReview*.

I would like to thank the reviewers for their earnest efforts in reviewing the manuscript. I accepted and responded step by step to all considerations by the reviewer improving the manuscript. The changes are highlighted by yellow.

**Reviewer 1**, Dr. Anna M Gorbacheva: Many thanks for her considerable comments. She made a detailed and comprehensive review. It seems that she knows the subject well and in depth. I suggest- if she wishes- to write a "Letter to the Editor" including all those interesting aspects and useful information in view of Endocrinology Research. In any case, we fulfilled all of her valuable suggestions thanking her again. Seven new references have been added (35,41,42,43,45,59,60) changing the order of preexisting references.

1. Title. I think so; it expresses accurately the aim of our paper. This manuscript is a MiniReview and focuses on the current management options for failure after surgery for primary hyperparathyroidism in view of a surgeon.

2. The Abstract has been shortened as suggested, but the instructions to authors do not include structured Abstract. Our unstructured Abstract is according to them.

3. Key-words. It has been done.

4. Introduction. a. Reference numbers. They have been done as shown Ref. 3 (page 4, line 22), Ref. 8 (page 4, line29).

b. Thank you for your comment for Vitamin D. I agree with you. Thus, it has been added "in patients without severe hypercalcemia" (page 5, line 20).

5. Diagnosis. a. I agree absolutely with you for FNA. Its use is restricted in selected cases as referred.



Cytology may reveal only cancer cells, nothing else.

b. Iodine-containing contrast. It has been added the text “ *The introduction of an iodine-containing contrast is contraindicated in cases where there is a decrease in the filtration function of the kidneys [12].*” (page 6, lines 25-27)

c. MRI. It has been added the text “*A recent study demonstrated that in addition to US and MIBI, noncontrast 3-Tesla MRI further increased the preoperative localization of pHPT (sensitivity of 92.0% [35, new Ref.]*.” (page 8, 3 last lines)

d. Scheme of diagnostic approach. It has been done as shown in figure 3.

c. Genetic diagnosis. “*especially in the context of MEN syndromes [41]. CDC73 gene mutations are not involved in the tumorigenesis of sporadic atypical parathyroid adenoma (APA) [38]. KMT2D might be a novel candidate driver gene that can be used as a diagnostic biomarker for parathyroid adenoma (PA). However, CDC73 mutations can be an early developmental event from PA to parathyroid carcinoma (PC) [42]. Germline mutations in CDKIs (the CDKN1B gene and CDKN2C gene) should be included in the genetic testing of patients with primary hyperparathyroidism [43, new Ref.]*.” (page 9, lines 22-29)

d. It has been added the text “ *In a multicenter study, two preoperative mathematical models predicted adenoma, atypical adenoma and parathyroid carcinoma with reliability, thus determining the choice of surgical plan. [45, new Ref.]*.” (page 10, lines 3-5).

6. Management. a. It has been corrected (diseased to affected gland). (page 10, line 14)

b. Recurrence. It has been added the text “*In the following studies, the recurrences occurred a long time after the first intervention. This means that the tumors probably developed de novo during the follow-up period and were not missed during the first operation.*” (page 10, 2 last lines; page 11, 2 first lines)

c. French study [46]. It has been clarified by adding the text “ *The predictive risk factors for failure of the initial parathyroidectomy and the need for reoperation shown by the multivariate analysis were cardiac history (congestive heart failure, arrhythmias, and valvular disease),*”. (page 12, 2 first lines). Cardiac history and other Elixhauser comorbidity index were included in the studied independent variables. By multivariate analysis among others, cardiac history and obesity were recognized as risk factors for failure and need for reoperation. The study was nationwide, published in the Annals of Surgery (the



second highest I.F. among surgical journals). It was an observation without other explanation, I can not explain this, only speculations someone may do.

d. The issue has been clarified *"In patients with histologically large normal parathyroid and pHPT, a controversial issue, excision exhibits a beneficial effect on PTH levels despite the higher risk of P-HPT/R-HPT than in adenoma or hyperplasia; thus, these patients need stricter biochemical postoperative follow-up [53]."*

(page 12, lines 13-16)

e. It has been added the text *"Intraoperative neuromonitoring is also a useful tool [9]."* (page 12, line 27)

f. The issue has been clarified *"(dwarf <300 mg or giant >3000mg)"* (page 13, line 3)

g. It has been added the text *"by its modulatory effect on systemic inflammation [57]."* (page 13, line 8)

h. It has been added the text *"by multivariable analysis"* page 13, line 9), *"The parathyroid glands are associated with glucose metabolism. PTH, insulin and osteocalcin interact by modulating insulin secretion and peripheral lipolysis [58]."* (page 13, lines 11-13)

i. Casanova test has been described by adding the text *"For this, the Casanova diagnostic test is useful. A tourniquet is applied to the arm, causing ischemia for 15 min, and PTH is measured. The test is positive when the PTH level is decreased to >50% of the preischemic value at 10 min after the end of ischemia. A decrease of <20% indicates a negative test. [59, new Ref.]"* (page 13, lines 17-20)

j. It has been added the text *"Antiresorptive drugs can also be used in the conservative management of patients with P-pHPT/R-pHPT [60, new Ref.]"* (page 13, lines 23-24)

k. It has been added the missed verb *"can be achieved"* (page 14, line 22)

l. It has been added the text *"ex vivo aspiration of the resected parathyroid tissue to confirm the presumed parathyroid tissue intraoperatively [7]."* (page 14, lines 6-7)

8. Scheme of treatment approach. It has been done as shown in figure 4 and figure 5.

11. Several new subheadings have been added as suggested changing the organization of the paper as well as language polishing.

## Reviewer 2

Many thanks for his positive comments.

I am sending the revised manuscript and hope to receive a favorable final decision.

We look forward to hearing from you at your earliest convenience.

Sincerely,



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