Dear Sirs,

Thank you for your recommendations and comments regarding the submitted manuscript. We greatly appreciate your interest in the topic and are happy to address each of the Editor's requests in the updated manuscript. Below you will find the Editor's suggestions in bold type and the authors' response. We hope that the updated manuscript addresses the Editor's recommendations satisfactorily.

Please do not hesitate to offer additional recommendations or concerns, as we strive to create a review that will be helpful to the readers.

Sincerely,

Tanaz Vaghaiwalla, MD

1. It is not clear to me if this is a retrospective cohort study (as the title would make me believe), a narrative review (as I assume), a systematic review (as a "review" may be) or a case-series (three cases described).
The Authors have updated our title which will make the intent of the article clear for the readers.
"Review of Intraoperative Parathormone Monitoring with the Miami Criterion: A 25-year experience"

2. I know it doesn't really matter in clinical practice, but I'm curious about which PTH assay was first developed by dr. Irvin and which one is used nowadays (whole PTH vs. intact PTH vs. third gen assay?). I would also like a brief comment on Point of Care (PoC) PTH assays: do you use them? Why you do or don't? I think this could go in the "Miami criterion" paragraph
The Authors have specified that in current practice a immunochemiluminescence assay is used.

"Since then, the intraoperative "quick PTH assay" has undergone many modifications since the original immunoradiometric assay developed by Dr. Irvin. In current practice, intraoperative PTH is measured using a rapid immunochemiluminescence assay."

"With the efficiency and speed of the intraoperative PTH assay, point of care testing which measures PTH at the bedside is not performed at this institution."

3. Abstract: a little more detail (ie: success rate) and focus on the Miami criterion (ie: definition and brief comparison with other criteria) would be welcome.

The Authors have included the definition and success rate of the Miami criterion within the address. The Authors have included the comparision with other criteria in the Longterm Outcomes section which is discussed below under comment 5.

"The Miami criterion is a protocol that uses a ">50% PTH drop" from either the greatest pre-incision or pre-excision measurement of PTH in a blood sample taken 10 minutes following resection of hyperfunctioning glands. Following removal of the hyperfunctioning parathyroid gland, a >50% PTH drop at 10 minutes indicates completion of parathyroidectomy, and predicts operative success at 6 months. IPM using the Miami criterion has demonstrated equal curative rates of >97%, which is comparable to the traditional approach, the bilateral neck exploration (BNE)."

4. I do not get how the first "example case" is different from the second one: if there are no major differences, delete either one. If there are differences worth to be noted, please point them out more clearly.
The Authors made the difference between the two case examples more clear.

"Unlike in the first case, the dramatic rise in pre-excision level, which was not observed in the previous example, suggests the surgeon has identified the hyperfunctioning parathyroid gland. During dissection, manipulation of the abnormal gland by the surgeon may have resulted in a sudden surge of PTH into the bloodstream reflected by a dramatic rise of pre-excision PTH level, it is important in this scenario to witness a drop in the PTH level on the subsequent 5 and 10 minute samples."

5. The mention of other criteria (Rome and Vienna) is very short: I'd really appreciate a more detailed comparison between the Miami criterion and these other criteria.
We have compared other criteria to the Miami criterion (Halle, Vienna, and Rome). We have also defined and compared Miami criterion to the Mayo.

"By obtaining PTH levels in real time and achieving a desired reduction, the surgeon may have greater confidence intraoperatively that the offending hyperfunctioning parathyroid gland has been excised. While IPM has become common practice in most experienced centers, the Miami criterion has been compared to other stricter protocols in predicting post-operative eucalcemia. Stricter criteria proposed include a larger >65-70% PTH drop and/or return of absolute PTH level to within normal limits, or a PTH decrease at 5 minutes after gland removal [26,27,28]. In comparison to other criteria, the >50% PTH drop was found to accurately predict operative success in >95% of patients who had IPM guided parathyroidectomy for pHPT. In fact, the Miami criterion demonstrated the highest accuracy in predicting operative success when compared to other protocols, which included the Vienna, Rome, and Halle criteria [27]. In a study, which applied stricter protocols, the false positive rate would be reduced; however, at the expense of a lower sensitivity and an increased false negative rate. This false negative rate would then result in performance of BNE that were not necessary for the patient [29].

An additional protocol from the Mayo clinic was compared to different criteria in a study of 1882 patients with pHPT who had parathyroidectomy with IPM [30]. The Mayo criterion defined a successful parathyroidectomy as >50% from baseline in addition to a normal or near-normal intraoperative PTH measurement at 10 minutes following removal of the abnormal gland. The Mayo criterion was compared with the following criteria for monitoring: a > 50% PTH drop at 10 minutes, > 50% PTH drop at 5 minutes, and intraoperative PTH within normal range at 10 minutes. The authors described an operative success of 97% equivalent to that of the Miami criterion. Results were similar when comparing Mayo criterion which had a sensitivity of 96%, PPV of 99%, and an accuracy of 95%, whereas the Miami criterion had had a sensitivity of 96%, PPV of 97%, and an accuracy of 94%. The criterion, however, differed with respect to MGD. Authors reported that MGD was found in 271 patients (14.5%). A total of 134 of 1858 patients (7.2%) were not able to meet criteria predictive of cure, which indicated the presence of MGD. The authors reported that using the >50% PTH criterion alone would have theoretically resulted in a failed parathyroidectomy in 22.4% of patients affected with MGD [30].”

An additional protocol from the Mayo clinic was compared to different criteria in a study of 1882 patients who underwent parathyroidectomy for primary hyperparathyroidism with IPM [30] The Mayo criterion defined a successful parathyroidectomy as >50% from baseline in addition to a normal or near-normal intraoperative PTH level at 10 minutes post excision. The Mayo criterion was compared with the following strategies for monitoring: a > 50% PTH drop at 10 minutes, > 50% PTH drop at 5 minutes, and normal intraoperative PTH levels at 10 minutes. The authors described an operative success of 97% equivalent to that of the Miami criterion. Results were similar when comparing Mayo criterion which had a sensitivity of 96%, PPV of 99%, and an accuracy of 95%, whereas the Miami criterion had had a sensitivity of 96%, PPV of 97%, and an accuracy of 94%. The criterion, however, differed with respect to MGD. Authors reported that MGD was found in 271 patients (14.5%). A total of 134 of 1858 patients (7.2%) failed to reach curative criteria which confirmed MGD. The authors reported that using the >50% PTH criterion alone would have theoretically resulted in a failed operation in 22.4% of patients affected with MGD [30].”

6. As a side note, please check that abbreviations are defined at their first use (ie: MIBI has been used in page 8 twice, but “explained” only in page 10; MGD was never stated to stand for multi-glandular disease, and so on) and check that all figures are referenced in the text.'

The Authors have reviewed the article and made the following changes. MIBI and MGD were described to be an abbreviation for Sestimibi and multigland disease, respectively. Additionally the PMID and DOI links were included for the references.