Author’s response to reviews

Title: Total parathyroidectomy with trace amounts of parathyroid tissue autotransplantation as the treatment of choice for secondary hyperparathyroidism: A Single-Center Experience

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Here is my response to the reviewers:

**Q: P.5, Line 2: patients and not cases**

**A:** Yes, it is patients not cases, a slip of pen.

**Q: P.5, Line 3: in all patients? How do you verify this? As far as I understand you suggest that this is a matter of calcitriol stosstherapy, why?**

**A:** Yes, these symptoms occurred in all patients, according to following up case history and drug history of all patients. Calcitriol stosstherapy is a kind of medical therapy following by nephrology doctors, which were recorded in patients’ case history.

**Q: P.5, L.12: I do not understand: P.4 you mentioned that this was a retrospective study. So, what the Ethic board had to prove? This was not a randomized trial. The decision about the operative procedure was strongly influenced by the nephrologist. 14 patients choose TPTX with AT. Were they listed for autotransplantation? As I understand 33 patients were not listed.**

**A:** This study was a retrospective research, not a randomized clinic trial. According to the regulation of our hospital, operations concerned with certain organs excision, including parathyroidectomy, should be approved by the Jinan Military General Hospital Research Ethics Board. As our hospital is one of the biggest kidney transplantation centers, there is large number of HTP
patients with serious condition and prolonged course who have indication of surgery. Distress of HTP disease suffered by the patients made strong subjective requirement of surgery. But their poor physical conditions bring high risk of surgery. Furthermore, in recent years contradictions and disputes of physician-patient are increasingly intensified, normative operation has been required more as a measure against lawsuits in China. So it is necessary of permission by Ethics Board in hospital before operation in addition to the patients’ strong subjective requirement.

Nephrologist made suggestions to the patients when surgery needed, but final decisions were made by patients.

After introduction of two operative procedures to the patients, it is the patients who choose the treatment, not listed.

**Q:** P6, L.10, Why CT scan was performed in 2 patients?

**A:** Surgical intervention in the form of parathyroidectomy is generally considered only in cases of severe SHPT. However, identification of the exact location of the parathyroid glands before parathyroidectomy is a challenge. We looked for parathyroid gland(s) in the neck using MIBI scintigraphy and US. The two patients could not find 4 parathyroids by ultrasonography and scintigraphy, so CT scan was utilized to identify exact number of parathyroid. The surgeon attended the ultrasonography examination, which was helpful to get an exact localization of parathyroid glands and made clear their relationship with the surrounding tissues.

**Q:** P6 surgical procedure: it is not necessary to describe the operative procedure. But I expect the following details: How often intraoperative ultrasound was performed? How often thyroid nodules were discovered.
How often gamma probe was performed, how often it was effective? I do not believe that in all 47 patients you find always one gland without nodular transformation.

A: According to preoperative and intraoperative localization, hyperplastic parathyroid was searched by gamma probe and visual observation, then excised sample was checked by gamma probe again, finally sample was indentified by microscopic examination as frozen-section in Department of pathology.

Gamma probe was utilized in every operation in this study. 133 of all parathyroids were detected as high examination value comparing with surrounding tissue.

Intraoperative ultrasound was not routinely used, but preoperative US examination was routinely used.

According to preoperative examination of thyroid, almost all thyroid glands perform as hyperplasia with nodular transformation. And nodular thyroid glands were not treated in the surgery without indication as malignant nodular by preoperative examination. In this study, 41 cases of 47 were diagnosed as nodular goiter in preoperation and intraoperation. And 1 case had a suspicion of malignant nodular by preoperative examination and after intraoperative pathological identification he was operated with total thyroidectomy.

Q: What were your criteria for intraoperative PTH?

A: The criterion for intraoperative PTH is 400 pg/ml. Internal medicine is effective in patients below 400 pg/ml of PTH on our experience.

Q: How do you estimate a weight of 30mg?

A: Transplanted tissue is weighted by electronic balance.
Q: Why do you choose the sterno-cleido-mastoid muscle for transplantation. This is not the standard site.

A: Sterno-cleido-mastoid muscle is not traditionally transplanted site. In this study sterno-cleido-mastoid muscle was adopted because: 1. transplanted operation on nearby muscle was much simple and convenient without another incision; 2. in the recurrent condition MIBI can localize lesion site; 3. quantity of transplanted tissue was small and muscle function was not influenced.

Q: P8 postoperative management. I miss the ionized calcium level, which is mandatory especially in patients on dialysis who show a low total calcium due to low albumin levels. Therefore, these patients can also be discharged with much lower total calcium levels when albumin corrected calcium or ionised calcium is measured. Which symptoms did the patients present? How many patients showed symptoms of hypocalcemia. Intravenous calcium substitution should be an exception and not a standard therapy.

A: Serum calcium includes ionized calcium and bound calcium. Ionized calcium level is tested in dialysis center, and bound calcium level utilized in this study is the biochemistry criterion for clinical relevance. Every patient after surgery show varying degrees hypocalcaemia, that presented dramatically as numbness or tetany seizures in hands, feet, corner of the mouth. In order to prevent and treat hypocalcaemia, calcium gluconate injection was administrated intravenously for 1 to 2 weeks, then oral calcium was treated in addition to 1,25 OH-Vitamin D3.

Q: What is the significance of 25-OH-Vit D3? I think it should be 1,25 OH-Vitamin D3.
A: Yes, it should be 1,25 OH-Vitamin D3. But, at present my hospital can't detect 1,25 OH-Vitamin D3.

Q: What was the sensitivity of ultrasound, intraoperative ultrasound, Mibi-scan, gamma probe, PTH assay?

A: This study was a retrospective research so sensation of each test was not statistically reported. Preoperative ultrasound test could localize abnormal neck mass generally, and MIBI test could further check parathyroid gland. Preoperative ultrasound and MIBI test was used when difficult to localize. Intraoperative PTH test could real time monitor surgery effects and guide post-surgery medication.

Q: P13. L1: which study is cited? There is a more actual paper of Tominaga from 2010 with 2660 patients.

Why do you not perform transcervical thymectomy, which is also a standard therapy? Sterno-cleido-mastoid muscle is not the standard site for autotransplantation in secondary hyperparathyroidism. The reason for choosing the brachio-radialis muscle is to be able to distinguish between a cervical recurrence and a graft depending recurrence, which is difficult for the sterno-cleido-mastoid transplant. We have extremely negative experiences with sterno-cleido-mastoid autotransplants: as hyperplastic autotransplants seem to spread all over the muscle a radical removal of the largest part of the muscle had to be performed in 4 patients. Graft dependant recurrences may develop even after 15 years. “ 42 months is a short observation period and therefore you cannot conclude that this
is a safe procedure. It can happen that 50% of your patients have recurrent disease after 5 years.

**A:** Ectopy parathyroid gland may exist in thymus gland. So in this study transcervical thymectomy was not performed if 4 parathyroid glands were excised; if not then did. Up to now there is no patient who got recurrence just because residual parathyroid gland in thymus and need further surgery.

Transplantation recurrence is related to quantitation of transplanted tissue. In this study sterno-cleido-mastoid muscle was adopted because: 1. transplanted operation on nearby muscle was much simple and convenient without another incision; 2. in the recurrent condition SPECT/CT can localize lesion site, $^{99m}$Tc-MIBI-SPECT/CT scan is to be able to distinguish between a cervical recurrence and a graft depending recurrence; 3. quantity of transplanted tissue was small and muscle function was not influenced. Actually up to now follow-up is as long as 5 years, and there is no recurrent patients we have met which may be relates to small quantitation of transplanted tissue we used.

30 pieces of 1 x 1 x 3 mm parathyroid tissue (transplantation weight is about 110 micrograms), we think the quantity of transplanted tissue is more. 10 pieces of 1 x 1 x 3 mm parathyroid tissue (weight is about 30 micrograms) is enough.