Author's response to reviews

Title: Pediatric differentiated thyroid carcinoma in stage I: risk factor analysis for disease free survival

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Author's response to reviews: see over
1. What were the indications for subtotal vs total thyroidectomy and could the authors present the follow-up data on the two groups separately?

**Answer:** We thank the valuable comment and revised our paper. Fundamentally, lobectomy was performed in patients with unifocal and unilateral tumor, no clinical lymphadenopathy, and no distant metastasis at diagnosis. Total thyroidectomy was performed in patients with multifocal or invasive tumor, clinical lymphadenopathy, or distant metastasis at diagnosis. However, subtotal thyroidectomy was performed to avoid critical complications, such as permanent hypoparathyroidism or bilateral recurrent laryngeal nerve (RLN) palsy, in selected patients who were basically candidates for total thyroidectomy. Unfortunately, we could not present the detailed follow-up data on the two groups (subtotal vs total thyroidectomy groups) separately in this study.

**Changes made in the manuscript:**
(Page 7. line 16-17) In selected patients who were basically candidates for total thyroidectomy. (Page 7. line 17-18) For example, patients presenting with ipsilateral RLN palsy underwent less total thyroidectomy to prevent bilateral RLN palsy.

2. What were the indications for neck dissections and how was the type of neck dissection chosen.

**Answer:** We thank the valuable comment and revised our paper accordingly. In this study, ipsilateral modified neck dissection (MND) was defined as systematic node dissection in the central compartment (level VI) and ipsilateral lateral compartment (level II to V). MND was usually performed in patients with advanced tumor stage or lymphadenopathy, however no or only central node dissection was performed in those with lower tumor stage or no lymphadenopathy.

**Changes made in the manuscript:**
(Page 7. line 18-Page 8. line 1) MND was usually performed in patients with advanced tumor stage or lymphadenopathy, whereas no or only central node dissection was performed in those with lower tumor stage or no lymphadenopathy.

3. Why was a chest X-ray performed in all patients?

**Answer:** We thank the helpful comment and revised our paper accordingly. All pediatric patients in this study underwent surgical treatments under total anesthesia. In Japan, all patients who are planed to have surgery under total anesthesia need to receive Chest X-ray examination as one of the preoperative routine examinations for total anesthesia. In addition, chest X-ray has been performed for screening purpose of apparent lung metastasis in all carcinoma patients (pediatric to older patients) at our institution. Accordingly, chest X-ray was performed preoperatively in all patients.

**Changes made in the manuscript:**
(Page 6. line 13-14) Chest X-ray was preoperatively performed as one of the routine examinations for total anesthesia and as a screening purpose of apparent lung metastasis in all patients.

4. Why was a CT scan performed since even with the presence of metastases of papillary carcinoma the treatment would still be total thyroidectomy and I131 treatment

**Answer:** We thank the valuable comment. This is a most significant problem for our clinical practice because we have quite different background to the use of radioactive iodine (RI). In Japan the use of RI is strictly controlled, and the number of centers that can perform RI treatment is very low. We therefore can not routinely include RI therapy in our treatment strategy. Such dilemma between appropriate treatment strategy and actual clinical practice in Japan is the issue to be resolved in the future. Thus, therapeutic RI treatment has principally been performed when refractory nodal recurrence was observed or when distant metastasis was detected visually by chest X-ray or CT scan.

5. What was the number of patients with follow-up less then 10 years?

**Answer:** We thank the helpful comments and revised the paper accordingly. The duration of follow-up was less then 10 years in 15 patients (26.3%).

**Changes made in the manuscript:**
(Page 4. line 19) In 42 patients (73.7%), the duration of follow-up was over 10 years.


**Answer:** We thank the helpful comment and revised the paper.
1. The title includes the words “TNM”, which may be deleted.

**Answer:** We thank the helpful comment and revised the title.

**Changes made in the manuscript:**

(Title) Pediatric differentiated thyroid carcinoma in stage I: risk factor analysis for disease free survival

2. The series extends over a long period of time with considerable developments in diagnostic ability, evaluation and the management of pediatric thyroid cancer. The philosophy of the extent of thyroidectomy, radioactive iodine and external radiation therapy has evolved during this time.

**Answer:** We thank the valuable comments.

Our strategy for pediatric thyroid cancer is basically no different both at previous and present time. Actually, diagnostic ability such as cytological or radiological evaluation for pediatric thyroid cancer has developed during the long time period. However, we have fundamentally performed thyroid resection in the following concept (lobectomy for patients with unifocal and unilateral tumor, no clinical lymphadenopathy, and no distant metastasis at diagnosis, and total thyroidectomy for patients with multifocal or invasive tumor, clinical lymphadenopathy, or distant metastasis at diagnosis). Therapeutic RI treatment has principally been performed when refractory nodal recurrence was observed or when distant metastasis was detected visually by chest X-ray or CT scan, because of the strictly limited use of RI in Japan.

3. The authors have 11 patients with follicular carcinoma of the thyroid. It is quite likely that, since this incidence appears to be quite high, some of these patients may have had a follicular variant of papillary thyroid carcinoma.

**Answer:** We thank the helpful comment.

To our knowledge, the incidence of PTC in pediatric patients ranged from 66% to 100% (over 80% in many studies) in the over 60 English literatures. The incidence in our study was 80.7% (46 PTCs including 2 follicular variant types of 57 DTCs). Pathological diagnoses in our series were reevaluated and confirmed. Therefore, the possibility of follicular variant of PTC was already excluded as well as Hürthle cell or insular type of thyroid carcinoma, medullary thyroid carcinoma, or anaplastic thyroid carcinoma.

4. The authors have reported local recurrence, which may be difficult to interpret since it could mean either local or regional recurrence.

**Answer:** We thank the valuable comments and revised the paper accordingly.

In this study, recurrent disease was defined as local recurrence (remnant thyroid tissue or regional lymph node) or metachronous distant metastasis that developed as new disease during the follow-up period, at least 6 months after the initial surgery. 26.3% (15 patients) exhibited
local recurrent disease. There were regional node recurrence in 13 patients and both remnant thyroid and regional node recurrence in 2 patients.

**Changes made in the manuscript:**
(Page 11. line 8-9) In the 15 patients (regional node recurrence in 13 and both remnant thyroid and regional node recurrence in 2), the clearance of local recurrences was achieved successfully.

5. Radioactive iodine treatment was used in only 10 patients. Generally, in the pediatric thyroid cancer group, radioactive iodine is used in a much higher percentage of patients.

**Answer:** We agree the valuable comment.
We have quite different background for RI therapy, as suggested. In Japan the use of RI is strictly controlled, and only a few centers can perform RI treatment. We therefore can not routinely include RI therapy in our treatment strategy. Such dilemma between suitable treatment and actual clinical practice in Japan needs to be resolved in the future. Thus, the purpose of the present study was to discriminate patients who were candidate for aggressive treatments (total thyroidectomy followed by RI therapy) from those who were not candidate for such treatments in stage I pediatric patients. Therefore, our results would become more important in the present Japanese clinical practice or other countries with similar problem because of the different use of RI.

6. In the abstract conclusion the authors have written “aggressive treatment should be considered for appropriate patients”. It is unclear what the authors mean by aggressive treatment.

**Answer:** We agree the helpful comments and revised the paper accordingly.
We consider that total thyroidectomy with node dissection followed by RI therapy is considered appropriate for patients with risk factor.

**Changes made in the manuscript:**
(Page 2. line 5-6. in the abstract conclusion). Aggressive treatment (total thyroidectomy, node dissection, and RI therapy) is considered appropriate for patients
(Page 16. line 11-12). Aggressive treatment (total thyroidectomy, node dissection, and RI therapy) is appropriate for stage I pediatric patients with risk factors

7. The overall size of the tumor reported is 4.3 cm, which is probably much larger than usually encountered in pediatric thyroid cancer.

**Answer:** We thank the valuable comments.
We do not know why the overall size of the tumor reported in this study is much larger than usually encountered in pediatric thyroid cancer. This may be due to 4 diffuse sclerosing PTCs, 11 FTCs, and 30 advanced tumor stage (T3 and T4a) carcinomas.

8. The authors have reported some experience with fine needle aspiration biopsy and suspected follicular thyroid carcinoma, which is not a common experience with FNA.

**Answer:** We thank the helpful comments.
Generally, FNA is not useful for diagnose of FTC, however the FNA results sometimes indicate the malignant suspicious of follicular neoplasms of the thyroid, although these are uncommon experience. We had such experience in only three FTCs. On the other hand, there were no any malignant suspicious by FNA findings in 6 FTCs, as suggested.

9. The subtotal thyroidectomy reported is unclear to this reviewer. Clearly, the time frame of this manuscript is quite large, however generally subtotal thyroidectomy is not a recommendation in suspected thyroid cancer.

**Answer:** We agree the valuable comments and revised the paper accordingly.
Fundamentally, lobectomy was performed in patients with unifocal and unilateral tumor, no clinical lymphadenopathy, and no distant metastasis at diagnosis. Total thyroidectomy was performed in patients with multifocal or invasive tumor, clinical lymphadenopathy, or distant metastasis at diagnosis. However, subtotal thyroidectomy was performed to avoid critical complications, such as permanent hypoparathyroidism or bilateral recurrent laryngeal nerve (RLN) palsy, in selected patients who were basically candidates for total thyroidectomy.

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