Risk Factor Stratification of Lung Metastasis in Children and Adolescent Papillary Thyroid Cancer

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Research Article

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Abstract

Background: Lung metastasis (LM) in pediatric papillary thyroid cancer (pPTC) is significantly higher than in adults. While spare information about pPTC and LM hampers to formulate specific guideline. Hence, we retrospectively analyzed the whole pPTCs in our center to investigate factors associated with LM and therapy outcomes.

Materials and Methods: PTCs with age≤20 years who received initial operations in ourcenterfrom December 2008 to December 2018 were retrospectively reviewed. Clinicopathological information, treatment pipelineand outcomes were analyzed retrospectively.

Results: Totally, 114 pPTC patients were enrolled in our study, LM was observed in 17 (14.9 %) cases. Significant risk factors associated with LM were age, sex, tumor size, multifocality, extrathyroidal extension, lymph node metastasis, number of metastatic lymph nodes (NMLNs)and postoperative stimulated thyroglobulin (sTg). NMLNs ≥14 was identified as an independent risk factor for LM by multivariate analysis (OR 25.166, 95% CI 2.814 - 225.009, $p = 0.004$) with a sensitivity of 86.7% and specificity of 81.1% for LM, which was verified by integrated meta-analysis. In terms ofresponse to radioiodine treatment in LM, 2 cases reached “excellent” response. “Biochemically incomplete”, “structurally incomplete” and “indeterminate” were in 3,12, 2 of 17 patients respectively. Postoperative sTg was correlated with the response to therapy of LM in pPTCs($p = 0.003$).

Conclusion: LM was frequently observed in pPTCs. NMLNs ≥14 was an independent risk factor for LM in our study and other cohorts, and postoperative sTg was a potential predictor for the therapy outcome of LM in pPTCs.

Synopsis

our study investigated the risk factor of lung metastasis in pediatric papillary thyroid cancer patients and try to find out the factors associated with therapy outcomes.

Introduction

Papillary thyroid cancer (PTC) is the most common endocrine malignancy in children and adolescents [1]. According to Surveillance, Epidemiology, and End Results (SEER) database, the incidence of pediatric papillary thyroid cancer (pPTC) has been increasing 9.56 % per year between 2006 and 2013 [2]. It accounts for about 1.4 % to 2.3 % of thyroid malignancies [3, 4]. Given the spare information about pPTC, American Thyroid Association did not publish the management guideline until 2015 [5]. However, majority of recommendations were based on recommendation in adult guideline. Inspired by the believe that children are not small adults [6], there is a large domain needing to be uncovered in pPTC. Being divergent from adult cases, pPTC tends to present with more aggressive features when diagnosed [7] and higher frequency of disease recurrence and persistence[8, 9] after surgery. Reportedly, pediatric patients are more

likely to have larger tumor size[10], higher portion of bilateral and multifocal lesions[11] and lymph node metastasis (LNM) that about 40–90 % in pediatric cases, compared to 20–50 % of adult cases[12].

Furthermore, lung metastasis (LM) was proved to be virtually risk factor for bleak prognosis in PTC patient. And LM happened in only 1–4% of adult cases [13], but was the leading cause of death. According to a long-term respective study [14], the 10-year mortality ratio of differentiated thyroid cancer (DTC) with LM in adults was 13.8 %, which was obviously higher than that of group without LM. Reportedly, LM was found in up to 30 % of pediatric patients [15–18]. Though majority of children typically demonstrate better RAI uptake than adults [5], few case would receive excellent response after serial I^{131} treatments [19, 20], and some of the young children had to suffer from the side effect, treatment-induced pulmonary fibrosis [21, 22].

Previous limited research has investigated the clinicopathological characteristics of pPTC patients and tried to identify risk factor of LM[3, 17, 20]. However, the data about children PTC was far less sufficient. Moreover, no information about children PTC from Chinese institution was reported and the factors related to response of RAI therapy in children has not been estimated [17]. Based on the consideration, we retrospectively analyzed the pPTC patients in our center to identify the risk factor of LM and response to treatment, which will be beneficial for pediatric guideline.

Methods

1. Study Population

We collected subjects from the prospectively maintained retrospective database in West China hospital. The inclusion criteria were: a. patients who initially received thyroid surgery in our institution from December 2008 to December 2018; b. patients who were younger than 20 years old [23, 24]; c. postoperative pathological diagnose was PTC independent of subtypes. The exclusion criteria were: a. postoperative pathological diagnose was follicular thyroid carcinoma, medullary thyroid carcinoma, or anaplastic thyroid carcinoma; b. patients had comorbidity with other cancer; c. clinicopathological and follow-up information was incomplete. This study was approved by the Institutional Review Board of West China Hospital of Sichuan University (No. 2020 − 737).

2. Clinical Management

The surgery was performed by two board-certified surgeons, and the histopathological reports were reviewed and confirmed by two experienced pathologists in a blinded manner independently. Based on the intraoperative findings and histopathological reports, every patient was staged by 8th edition AJCC/TNM staging system [25]. Recurrence was defined as new biochemical, structural, or functional evidence of disease that was detected following any period of remission[24] [26]. Minimal extrathyroidal extension (mETE) was defined as extension to the perithyroidal soft tissue or strap muscles, gross

extrathyroidal extension (gETE) was defined as extrathyroidal extension (ETE) beyond the strap muscles [27].

I^{131} was administrated to patients with locoregional or nodal disease that cannot be resected or distant metastases [5]. The patients received RAI therapy after withdrawing levothyroxine for 3 weeks. Neck ultrasound and pulmonary Computed Tomography (CT) scan were performed, and serum thyroglobulin (Tg), anti-Tg antibodies (TgAb), TSH, free T3 (FT3) and free T4 (FT4) were measured to evaluate the disease status. According to the report of the nuclear medicine department of our hospital [28], activity was administered on a weight basis (1.35–2.7 mCi/kg) for prepubertal patients. Activity administered after puberty ranged from 100mCi to 200mCi (100mCi for simple remnant ablation, 150mCi – 200mCi for postoperative residual neck lymph node metastasis or distant metastasis).

3. Follow Up

All patients were usually followed 1, 3, 6, and 12 months after surgery during the first year. Then they were regularly followed up every 6–12 months. Dynamic surveillance of Tg, TgAb, thyroid hormones, cervical ultrasonography and chest CT are routinely performed [5, 29] .

4. Definitions Of Therapy Outcome

The response to RAI therapy of LM patients was divided into four categories according to adults ATA guideline: a. Excellent response (ER) (negative imaging and Tg<0.2 ng/ml or postoperative stimulated thyroglobulin (sTg) <1ng/ml, with TgAb<40 IU/ml); b. Biochemical incomplete response (BIR) (negative imaging and Tg > 1 ng/mL or sTg > 10 ng/mL or rising TgAb); c. Structural incomplete response (SIR) (persistent or newly identified loco-regional or distant metastases regardless of Tg or TgAb levels); d. Indeterminate response (IR) (biochemical or structural findings which cannot be classified as either benign or malignant) [29].

Statistics Description

Statistical analysis was performed using SPSS software, version 21.0 (SPSS, Chicago, IL, USA). Chi-square test or Fisher's exact were used to compare categorical variables. T-test or Mann-Whitney U test were performed to compare the parametric and nonparametric continuous data. Univariate and multivariate Cox regression was performed to identify the independent risk factor of LM. A receiver operator characteristic (ROC) curve analysis was used to determine the optimal cut-off points for predicting LM and therapy outcome in pPTC patients. *p*-value < 0.05 was considered indicative of statistical significance.

Results

1. Patients' Characteristics

As the small portion of the pediatric thyroid cancer, a total of 114 subjects were enrolled in our final analysis by the flowchart (Figure S1) of inclusion and exclusion, including 91 female (79.82 %) and 23 males (20.17 %) (ratio: 3.96:1) with mean diagnosis age 16.49 ± 3.23. The median follow-up time was 64.50 months (range, 20–140 months). 17 (14.91%) out of 114 pPTC patients had LM (13 patients were diagnosed at first visit, 4 appeared during follow up). Significant demographic difference was detected between presence and absence of LM groups (Table 1), cases with LM were significantly younger (14.16 ± 3.29 vs 16.49 ± 3.23, $p = 0.007$) and more male patients (41.17 % vs 16.49 %, $p = 0.044$). Moreover, significantly more aggressive clinicopathological characteristics presented in LM group - lager tumor size (39.81 ± 14.66 mm vs 23.20 ± 15.22 mm, $p < 0.001$), multifocality (93.75 % vs 34.73 %, $p < 0.001$), ETE (gross and minimal) (88.24 % vs 31.06 %, $p < 0.001$) and number of metastatic lymph nodes (NMLNs) (23 vs 9, $p < 0.001$). In addition, postoperative sTg level was significantly higher (1256.70 ± 1421.60 ng/ml vs 17.52 ± 33.89 ng/ml, $p = 0.008$) in LM presence group than in LM absence group. Therefore, it is obvious that LM presence cases intend to be more aggressive. As continuous variables, diagnosis age, tumor size and NMLNs showed excellent predictive value for LM (AUC = 0.73, 0.79 and 0.84, respectively) (Table S1, Figure S2). Being different from PTC in adults, tumor size that downscaled from 4 cm to 2cm was associated with LM. It implied different nature between pPTC and adult one. Given that previous studies had fully demonstrated the postoperative sTg was significantly related with LM [20] [24] [23], which was consistent with our study. Therefore, we did not perform the further analysis about sTg.

Table 1
Characteristics of patients with and without lung metastasis

Characteristic	No lung Metastases (N = 97)	Lung Metastases (N = 17)	Total (N = 114)	*p*
Age at diagnosis (years) (Mean ± SD)	16.49 ± 3.23	14.16 ± 3.29	16.14 ± 3.33	0.007 [a]
Age <16	29(29.89)	12(70.58)	41(35.96)	0.001 [a]
Age 16–20	68(70.10)	5(29.41)	73(64.03)	
Female	81 (83.51)	10(58.82)	91 (79.82)	0.044 [a]
Male	16 (16.49)	7(41.17)	23 (20.17)	
Tumor size (mm) [#1]	23.20 ± 15.22	39.81 ± 14.66	25.66 ± 16.19	<0.001 [a]
≤ 2cm	53 (54.64)	1 (5.88)	54 (47.37)	<0.001 [a]
>2cm	44 (45.36)	16 (94.12)	60 (52.63)	
Multifocality (yes/no)[#2]	33/62(34.73/65.26)	15/1(93.75/6.25)	48/63 (43.24/56.75)	<0.001 [a]
Histology types				
Classic PTC	85(87.62)	14(82.35)	99(86.84)	0.274
Follicular variant PTC	6(6.18)	3(17.65)	9(7.89)	
Diffuse sclerosing variant	4(4.12)	0(0)	4(3.50)	
Undefined	2(2.06)	0(0)	2(1.75)	
Hashimoto's thyroiditis(yes)	27(27.83)	1(5.88)	28(24.56)	0.102
Nodular goiter	38(39.17)	4(23.53)	42(36.84)	0.217
Extrathyroidal Extension[#3]				
Introthyroidal	56(58.94)	2(11.76)	58(51.78)	<0.001 [a]
Minimal ETE	31(32.63)	1(5.88)	32(28.57)	
Gross ETE	8(8.42)	14(82.35)	22(19.64)	

Abbreviations: PTC, papillary thyroid cancer; ETE, extrathyroidal extension; NMLNs, number of metastatic lymph nodes; sTg: postoperative stimulated thyroglobulin. [a]: statistically significant difference; [#1] : six patients have no known data of tumor size; [#2]: three patients have no known data of multifocality; [#3]: two patients have no known data of extrathyroidal extension; [#4] : included cases who received RAI and excluded thyroglobulin antibody>40 IU/mL cases, 51 date were available.

Characteristic	No lung Metastases (N = 97)	Lung Metastases (N = 17)	Total (N = 114)	*p*
LN metastasis				
pN0	13(13.40)	1 (5.88)	14 (12.28)	0.002 [a]
pN1a	36(37.11)	0(0.00)	36(31.58)	
pN1b	48(49.48)	16 (94.12)	64(56.14)	
NMLNs	9	23	11	<0.001 [a]
sTg(ng/mL)[#4]	17.52 ± 33.89	1256.70 ± 1421.60	339.70 ± 892.90	0.008 [a]
Median follow-up time(months)	64.5(20–140)			

Abbreviations: PTC, papillary thyroid cancer; ETE, extrathyroidal extension; NMLNs, number of metastatic lymph nodes; sTg: postoperative stimulated thyroglobulin. [a]: statistically significant difference; [#1] : six patients have no known data of tumor size; [#2]: three patients have no known data of multifocality; [#3]: two patients have no known data of extrathyroidal extension; [#4] : included cases who received RAI and excluded thyroglobulin antibody>40 IU/mL cases, 51 date were available.

2. Predictors Of Lung Metastasis

To define the virtual independent risk factor of LM in pPTC patients, we performed further analysis. On multivariate analysis, NMLNs>14 was an independent predictor for LM (OR 18.19, 95% CI 1.18–280.13, $p = 0.038$, Table 2) after adjusted by age, sex, tumor size, ETE and multifocality. Grouped by NMLNs (>14, ≤ 14), and the rate of LM in patients with NMLNs >14 was significantly higher than that in ≤ 14 group (42.9 % vs 2.5 %, $p<0.001$, Fig. 1A). In order to double validate our analysis result, we performed meta-analysis with previous reported results. Meta-analysis revealed that N1b was associated with an increased risk of LM (summary OR = 6.33, 95% CI = 3.23–12.41) without significant heterogeneity ($p = 0.46$, $I^2 = 0\%$) (Fig. 1B). Furthermore, combined with the only one previous research [17] that discussed the exact number of metastasized lymph node in pPTC, the integral result showed that NMLNs had higher odd ratio (summary OR = 12.66, 95% CI = 8.81–16.51) (Fig. 1B). Accordingly, NMLNs was identified as a significant risk factor for LM, which was validated by integrated analysis.

Table 2
Univariate and multivariate analyses of clinicopathological factors affecting lung metastasis

	univariate analyses			multivariate analyses		
Characteristic	OR	95% CI	*p*	OR	95% CI	*p*
Age 16–20	REF	REF	REF	REF	REF	REF
Age ≤ 16	5.63	1.82–17.42	0.003 [a]	1.22	0.13–11.70	0.86
Female	REF	REF	REF	REF	REF	REF
Male	3.54	1.17–10.69	0.025 [a]	1.82	0.20-16.56	0.60
Tumor size ≤ 21mm	REF	REF	REF	REF	REF	REF
Tumor size>21mm	21.32	2.69- 168.31	0.004 [a]	0.53	0.02 15.50	0.71
Multifocality (no)	REF	REF	REF	REF	REF	REF
Multifocality (yes)	28.18	3.56-222.85	0.002	6.46	0.47–88.36	0.16
Introthyrodial	REF	REF	REF	REF	REF	REF
Minimal ETE	0.903	0.079–10.37	0.935	0.61	0.02–18.20	0.78
Gross ETE	49.00	9.35-256.79	<0.001 [a]	28.11	0.95-830.67	0.053
NMLNs ≤ 14	REF	REF	REF	REF	REF	REF
NMLNs>14	27.44	5.68-132.56	<0.001 [a]	18.19	1.18–280.13	0.038 [a]

Abbreviations: ETE, extrathyroidal extension; Minimal ETE: extension to the perithyroidal soft tissue or strap muscles; Gross ETE: extension beyond the strap muscles; NMLNs, number of metastatic lymph nodes. OR, odds ratio. CI, confidence interval. [a]: statistically significant difference.

3. Clinicopathological And Therapy Outcomes In Pediatric Lung Metastasis Patients

Since few information has been uncovered in previous studies, we showed the detailed clinicopathological and therapy outcomes of the 17 LM patients (Table S2). In 17 patients, 10 were females and 7 males. The median cumulative RAI activity was 600 mCi (range 250–900 mCi), and the median total number of RAI courses was 3 (range 2–5). Due to 2 cases were lost in follow-up, 15 patients' information was used for further analysis. Size of metastasized tumor on the imagine of pulmonary CT scan increased obviously in 4 (26.67%) cases (No. 1,6,11,14) after surgery and RAI therapy, significantly

decreased in 7 (46.67%) cases (No. 2, 3, 4, 5, 7, 8, 10), unchanged in 3 (20.00%) cases (No. 9, 12, 15) and undetected in 1 (6.67%) case (No. 13) (but can be detected on the I^{131} diagnostic whole-body scan) (Fig. 2A). The dynamic change of LM size was consistent with their Tg change (Fig. 2B). 2 (13.33 %) cases received ER, 3 of 15 (20 %) patients were BIR, and the rest (10 of 15, 66.67 %) was SIR (Fig. 2C). Given the small number of LM pPTC patients, it barely had sufficient statistic power to discriminate risk factor by multivariate analysis. Therefore, we performed univariate comparison in Table S3. SIR was intended to be associated with the higher postoperative sTg value (141.4 vs 1167.0 IU/mL, $p = 0.003$), and ROC curves showed that postoperative sTg ≤ 307 IU/mL had excellent sensitivity and specificity (100 % and 0 % respectively, $p = 0.001$) for patients who achieved excellent or BIR (Fig. 3A). Moreover, the rate of SIR in postoperative sTg >300 IU/mL group was 100% which is significantly higher than that in sTg ≤ 300 IU/mL group (0 %) ($p<0.001$, Fig. 3B).

Discussion

In the present study, we found that 14.9 % patients (17 / 114) pPTC had LM and further identified the risk factor of LM and response to treatment in pediatric patients. By univariate comparison, younger age, male, lager tumor size, multifocality, ETE, the LN metastases, and postoperative sTg were associated with LM, which was consistent with the previous results[18, 20]. Furthermore, we identified NMLNs>14 as independent risk factor for LM in pPTCs with sensitivity and specificity of LM (92.3% and 97.3% respectively). And the incidence of LM between the two groups (NMLNs >14, NMLNs ≤ 14) was significantly different (42.9% vs 2.5%, $p<0.001$). Previously, few studies [3, 17, 18, 20] had explored the relationship between metastasized lymph nodes and LM in pPTC patients. And only one [17] investigated the exact metastasized number of lymph node. The result in our cohort was consistent with all of them by integral meta-analysis. Therefore, we should not only pay attention to the extent of metastasized lymph node, but also the exact number in pPTC patients.

It has been suggested that the genetic features of pediatric patients was different from adults [30–32]. The $BRAF^{V600E}$ mutation occurred in 27–83% of adult PTC cases, and was associated with the aggressive tumor features and poor outcome[32, 33]. However, the frequency of $BRAF^{V600E}$ was about 19% in pediatric patients[34], which was significantly lower. Therefore, it is interesting to explore the relationship with tumor features in pediatric patients in the future[31]. Meanwhile, fusion genes such as RET/PTC, ETV6-NTRK3 and BRAF fusions (AGK-BRAF and AKAP9-BRAF) [34, 35] [36, 37]are more likely discovered in pediatric cases, and was associated with aggressive clinicopathological characteristics. However, several studies suggested that fusion genes were more common than single point mutations in children PTCs, but they did not correlate with aggressive tumor features[31, 38, 39]. Therefore, if the molecular change associated with the tumor features there is still no definite conclusion, which needed more further studies.

For LM patients, radioiodine is indicated for treatment of iodine-avid distant metastases [40]. Most children with asymptomatic and nonprogressive I^{131}-refractory disease can be safely monitored while continuing TSH suppression. If the disease progressed persistently, systemic treatment, tyrosine kinase

inhibitor (TKI) may be considered [5]. *Mahajan P.* et al, reported that 3 children with metastatic PTC not amenable or refractory to RAI, but responded to Lenvatinib [41]. And the safety and effectiveness of Vandetanin was also reported in advanced pediatric medullary thyroid carcinoma patients [42]. In our cohort, there is one case (No.7) who was refractory to RAI received targeted therapy. But the response is limited, and the patient is suffering the serious adverse effect at the same time. Hence, TKI therapy is worthy to be explored in further study or clinical trials.

The study was limited by retrospective nature and the small sample size (114 cases and 17 LM cases), though the sample size is similar as previous reports [17, 18, 20]. Therefore, multi-center with large sample size study is urgently expected to explore and validate the uncertain and current findings. Moreover, genetic mutation is expected to be revealed if apparatuses available.

In conclusion, pPTC patients tend to present more aggressive features than adults. And NMLNs >14 is an independent predictor for LM, which was consistent with previous reports. In addition, postoperative sTg was associated with the radioiodine therapy outcome in LM. However, considering the small sample size, the result should be interpreted cautiously in other study and region.

Declarations

Author contributors: Liying Wang and **Feng Liu**: Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing. **Zhihui Li** and **Han Luo**: conceptualization, study design. **Lingyun Zhang, Shu Rui, Yang Liu, Wanting Liu** and **Feiyang Shen**: Data acquisition; **Rui Huang, Tao Wei, Rixiang Gong and Jingqiang Zhu**: Quality control of data and algorithms.

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Figures

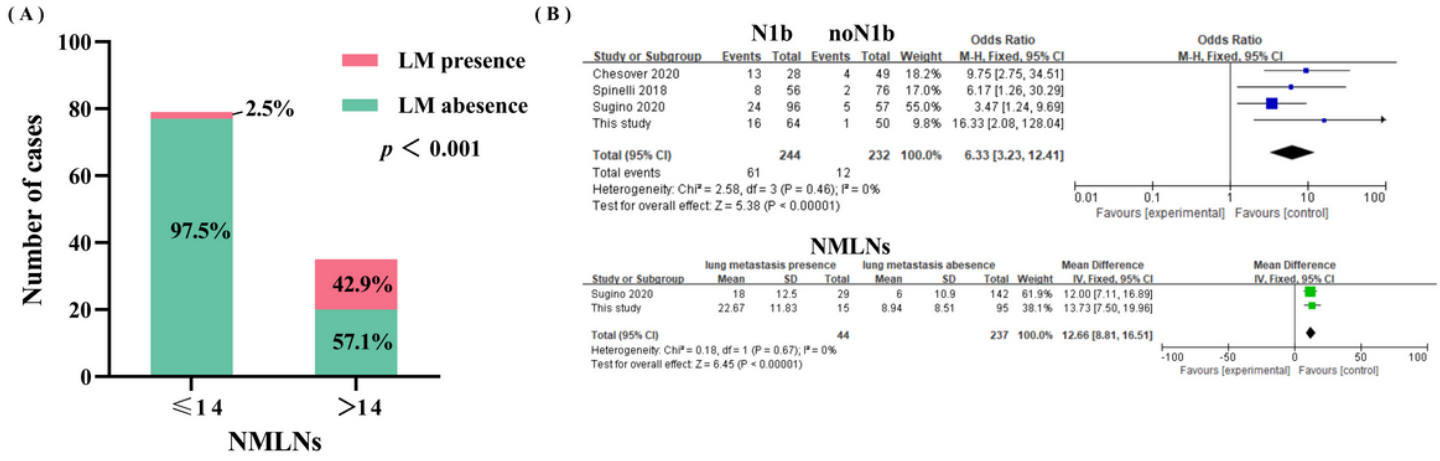

Figure 1

A. The different frequency of lung metastasis in group NLMNs 14 and group ≤ 14; B. Forest plot showing association of N1b and NLMNs in pediatric thyroid cancer with distant metastasis. Abbreviations: NLMNs, number of metastatic lymph nodes; N1b, positive lateral compartment lymph node metastasis; no N1b, negative lymph node metastasis or central compartment lymph node metastasis; O , odds ratio. CI, confidence interval.

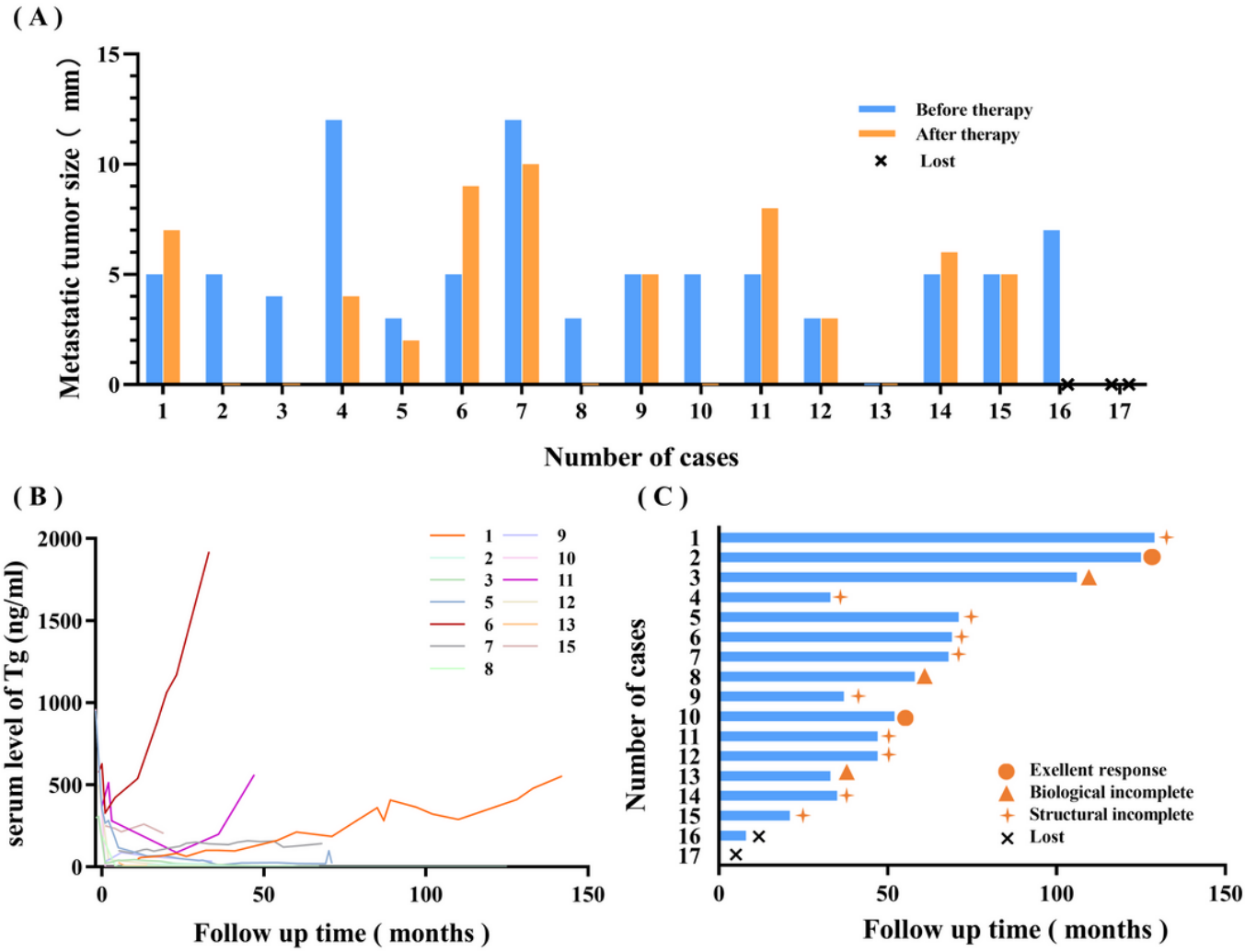

Figure 2

A. Change of metastasis tumor size on the imagen of pulmonary CT scan before and after therapy. The detail date of metastasis tumor size of case 16 and case 17 were lost; B. Dynamic change of serum level of Tg during the follow up. Case 14 was excluded because of abnormal level of thyroglobulin antibody. Case 4, case 16 and case 17 were excluded because of lacking data of serum Tg level. C. Final response outcome after therapy of every case. There are 2 cases receiving excellent response, 3 cases receiving biological incomplete response (disease disappeared on the imaging examination and value of serum Tg ≤1 ug/L) and 10 cases receiving structural incomplete response. Therapy outcomes of case 16 and 17 were unknown. Abbreviations: Tg, thyroglobulin;

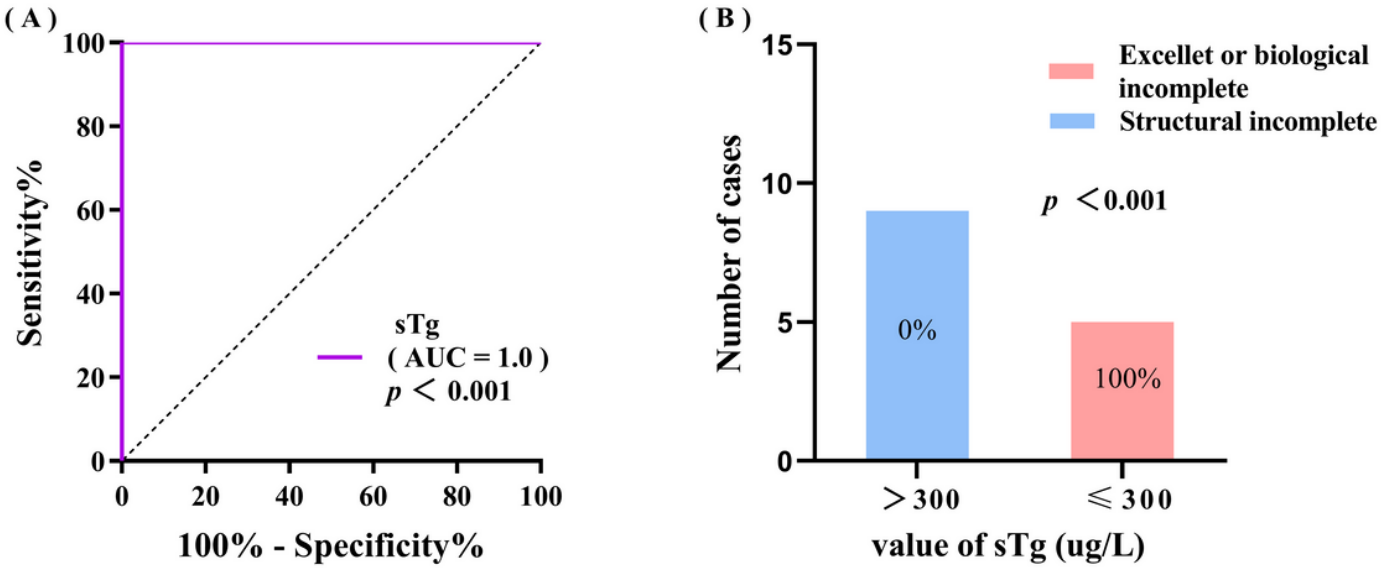

Figure 3

A. Receiver operating characteristic curve analysis of postoperative sTg and therapy outcome of lung metastasis pPTC patients. Area under the curve 1.0 [CI 1.0 - 1.0], p = 0.003. CI, 95% confidence interval; B. The different percentage of therapy outcomes between two groups(sTg≤300 IU/mL and>300 IU/mL).

Supplementary Files

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