Efficacy analysis of $^{131}$I therapy and predictive value of preablation stimulated thyroglobulin for lung metastases from differentiated thyroid cancer

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Abstract

Objective. – Our objective was to investigate the clinical efficacy of $^{131}$I therapy for lung metastases from differentiated thyroid cancer (DTC) and assess whether the preablation stimulated thyroglobulin (Tg) could have predictive value for the outcome. Methods and materials. – Fifty-two DTC patients (mean 44.5 ± 19.2 years; 33 females and 19 males) with lung metastases treated with $^{131}$I were retrospectively analysed. The therapeutic efficacy was evaluated based on the change in serum Tg. Fifty patients’ preablation stimulated Tg were collected with negative Tg antibody levels and estimated using the t-test method. Results. – After $^{131}$I therapy, a significant decrease in serum Tg was seen in 30 patients (effective rate, 57.6%), and changes in serum Tg that indicated stabilization and ineffectiveness were both seen in 11 patients (21.2%). Only patients with age under 45 years were more likely to respond to serum Tg changes ($P=0.046$). But binary logistic regression revealed that none of the six factors (age, patient gender, pathological type, local lymph node involvement, size of metastases, and $^{131}$I uptake by metastases) had statistically significant impacts on the efficacy analysis ($P>0.05$ for all the factors). For analysing with the preablation stimulated Tg, the “Fine miliaric” and $^{131}$I uptake positive with great prognosis group was much lower than any other group ($P<0.05$). Conclusion. – $^{131}$I therapy is a feasible and effective treatment for DTC lung metastases. A better prognosis would be accomplished in those who had low level of preablation stimulated Tg in DTC patient with lung metastases.

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Résumé

Objectif. – Examinons l’efficacité du traitement par iode-131 du cancer thyroïdien différencié avec métastases pulmonaires et déterminer la valeur prédictive du taux de la thyroglobuline stimulée avant résection. Méthodes. – Analyse rétrospective de 52 patients (âge moyen 44,5 ± 19,2 ans ; 33 femmes ; 19 hommes) présentant des métastases pulmonaires d’un cancer thyroïdien différencié et traités par l’iode-131. L’évolution du taux plasmatique de la thyroglobuline (Tg) a permis l’évaluation de l’efficacité thérapeutique. Le taux de Tg stimulée était déterminé avant la résection chez 50 patients sans anticorps anti-Tg et sa valeur prédictive estimée avec le t-test. Résultats. – Chez 30 patients, le traitement par iode-131 est suivi d’une diminution significative de la Tg plasmatique (57,6 % d’efficacité) ; une inefficacité du traitement et une stabilisation du taux plasmatique de la Tg sont notées chez 11 patients (21,2 %). Si la probabilité de répondre au traitement avec une modification du taux plasmatique de la Tg n’est augmentée que chez les patients âgés de moins de 45 ans ($P=0.046$), l’analyse par régression logistique binaire ne retrouve pas d’influence significative des six facteurs étudiés (âge, sexe, type histologique, invasion ganglionnaire locale, taille des métastases, fixation de l’iode-131 au niveau des métastases) ($P>0.05$ pour tous les facteurs). L’analyse des taux de Tg stimulée avant résection montre un meilleur pronostic uniquement dans le groupe « miliaire » fixant l’iode-131. Conclusion. – L’iodothérapie est un traitement efficace pour le cancer thyroïdien différencié avec métastases pulmonaires. Le pronostic serait meilleur chez les patients ayant un faible taux de Tg stimulée avant résection.

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Lungs and bones are the most common distant metastases sites for differentiated thyroid cancer (DTC) [1,2]. And those, which develop distant metastases always have worse prognosis, though DTC usually has a low mortality [3–5]. Comparing with bone metastases, ¹³¹I has been an effective measure of treating lung metastases from DTC. Because ¹³¹I therapy can partly or completely eliminate lung metastases of DTC. But a systematic review recently confirmed that the majority of paediatric and adolescent patients with DTC and pulmonary metastases treated with ¹³¹I do not achieve complete response to therapy [6]. But the exact therapy efficacy is still controversial.

As we all know, thyroglobulin (Tg) level is very important in DTC patients’ follow-up. Elevated Tg after thyroidectomy and radioiodine remnant ablation suggests persistence or recurrence of viable tumor tissue. But little is known about the preablation stimulated Tg, which reflects the Tg level stimulated by high-level thyroid-stimulating hormone in patients preparing for ¹³¹I remnant thyroid ablation 2 or 4 weeks immediately after thyroidectomy or after levothyroxine withdrawal. Some researchers [7,8] reported that it has predictive value of metastases. But most researchers do not believed because of residual thyroid tissue [9,10].

Therefore, this retrospective study wanted to evaluate the usefulness of ¹³¹I therapy for lung metastases from DTC. At the same time, we also investigated whether the predictive value of preablation stimulated Tg could have a potential prognostic value to predict the outcome in this study.

1. Materials and methods

1.1. Diagnostic criteria for DTC lung metastases

The diagnosis of DTC lung metastases has been established based on thyroid tumor pathology, clinical symptoms, serum Tg, and Tg antibody (TgAb) when the serum TSH level is at least 30 mIU/L after 3–4 weeks of T4 withdrawal. ¹³¹I whole-body scan (WBS) and ¹³¹I-SPECT/CT after ¹³¹I therapy, ¹⁸F-FDG SPECT or PET/CT, X-rays, CT. The diagnosis of DTC lung metastases can be confirmed by the following approaches: criterion 1, ¹³¹I-WBS demonstrates ¹³¹I uptake in lateral or bilateral lungs with or without other image positive results; criterion 2, positive PET finding confirmed with chest CT or positive PET/CT in lung; criterion 3, ¹³¹I-WBS and PET was negative, but anatomical imaging (X-rays, CT) was positive and Tg level was abnormal. The metastases detected only by ¹³¹I-WBS, with negative findings at X-rays or chest CT, were defined as “fine miliaric” and as “nodular” the metastases detected by any radiological technique available at the time of observation, independently of ¹³¹I-WBS results [11].

1.2. Clinical data for DTC lung metastases

1.2.1. Patients

More than 5000 patients with DTC were admitted to the Department of Nuclear Medicine of Xinhua Hospital, Shanghai Jiaotong University between Nov. 1980 to Jan. 2011. All patients were examined retrospectively and evaluated according to the results of clinical examination and routine nuclear medicine methods (serum Tg, and TgAb when the serum TSH level is at least 30 mIU/L after 3–4 weeks of T4 withdrawn. ¹³¹I-WBS and ¹³¹I-SPECT/CT after ¹³¹I therapy, ¹⁸F-FDG SPECT or PET/CT, X-rays, CT, neck ultrasound). Of these patients, according to the criteria, 54 had lung metastases but two patients’ data were missing. So there were 52 lung metastases from DTC collected into this study: follicular thyroid carcinoma (FTC) occurred in 4/52 and the other 48/52 were all papillary thyroid carcinoma (PTC). Age at first diagnosis of the 52 patients ranged from 6 to 81 years (mean 44.5 ± 19.2 years; 33 females and 19 males). Six patients were children (age ≤ 18 years, mean 12.8 ± 4.4 years; 4 females and 2 males). Characteristics of study subjects are presented in Table 1.

1.3. Methods of ¹³¹I therapy and post-treatment ¹³¹I-WBS

All patients underwent ¹³¹I therapy 3 to 5 weeks after thyroidectomy, with no replacement therapy or levothyroxine withdrawal as well as low-iodine diet [12]. TSH levels increased to at least 30 ng/mL. A total of 3.7–67.57 GBq (100–2500 mCi) ¹³¹I was given to each patient. In the presence of persistent functioning lung metastases, radioiodine therapy was repeated periodically (first to second 3 months and at least 6 months after the second therapy, then about 1 year after fifth or sixth therapy according to the conditions of the patients). Given dose was 4.05–8.11 GBq (150–300 mCi) each time for the lung metastasis.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>52</td>
</tr>
<tr>
<td>Age (y) mean ± SD</td>
<td>44.52 ± 19.16</td>
</tr>
<tr>
<td>Range</td>
<td>30–81</td>
</tr>
<tr>
<td>Median</td>
<td>47</td>
</tr>
<tr>
<td>Gender (M/F ratio 1: 1.74)</td>
<td>Male 19 (36.54%) Female 33 (63.46%)</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Papillary 48 (92.31%) Follicular 4 (7.69%)</td>
</tr>
<tr>
<td>Local lymph node involvement</td>
<td>Yes 40 (76.92%) No 12 (23.08%)</td>
</tr>
<tr>
<td>Size of lung metastases</td>
<td>Fine miliaric 34 (65.38%) Nodular 18 (34.62%)</td>
</tr>
<tr>
<td>¹³¹I uptake by lung metastases</td>
<td>Positive 41 (78.85%) Negative 11 (21.15%)</td>
</tr>
<tr>
<td>Follow-up (y) mean ± SD</td>
<td>44.52 ± 19.16</td>
</tr>
<tr>
<td>Range</td>
<td>1.5–31.1</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
</tr>
</tbody>
</table>
patients. Children were given lower dose than adults. Patients combined with other metastases (especially bone) were given highest dose.

A post-treatment $^{131}$I-WBS, with planar images in anterior and posterior projections, was performed 5 days after $^{131}$I therapy. A large field-of-view gamma camera equipped (Philips Precedence 16 SPECT/CT, Philips, Netherlands and Infinia Hawkeye H3000YS SPECT, GE, United States) with a high energy (peak energy centred on 360 keV with a 20% energy window). Questionable lung metastasis was performed SPECT/CT to classify with other non-pulmonary metastases (for example, ribs, sternum and thoracic vertebrae, etc.).

1.4. Protocol for routine follow-up

Lung metastases patients were routinely given $^{131}$I at least two times as mentioned above. Thyroid hormone withdrawal and low-iodine diet protocols were applied for about 4 weeks. Tg and TgAb, chest CT, neck ultrasound and $^{18}$F-FDG SPECT or PET/CT were obtained continuously for follow-up 6 months for the first and second time, 1 year for the third time and 2 years for the fourth time. Tg and TgAb levels were measured by an immunoradiometric method (provided by Shanghai Institute of Biological Products Company, Shanghai, China). The follow-up period was 1.5–31.1 years with a median follow-up of 3.0 years.

1.5. Evaluation criteria for changes in serum Tg after $^{131}$I therapy [13]

The results of evaluation were classified into three types, including effectiveness, stabilization and ineffectiveness. For effectiveness, after $^{131}$I therapy was repeated at least three times, the serum Tg significantly decreased. Compared with pre-treatment, the serum levels of Tg exhibited a reduction of at least 25% after the last treatment, which was considered effective. For stabilization, after at least three $^{131}$I treatments, stability was achieved if the serum Tg decreased or increased less than 25% after the last treatment compared with pre-treatment. For ineffectiveness, significantly elevated serum Tg was observed after at least three $^{131}$I treatments; when compared with pre-treatment, the serum Tg increased at least 25%. This finding was defined as ineffective.

1.6. Statistical analysis

SPSS version 18.0 was used for statistical analysis. Univariate analysis of the significance of the data available was performed. Binary logistic regression analysis was used to determine which factors contributed to the outcome of $^{131}$I therapy response. $t$-test was used for preablation stimulated Tg. Two-sided $P$ values $<$ 0.05 were considered to indicate statistical significance.

2. Results

An outline of the cases studied is given in Table 1. The parameters considered in our analysis were: age at cancer diagnosis ($\geq$ 45 and $<$ 45 years), gender, histological type (papillary, follicular), local lymph node involvement, size of metastases (fine miliaric or nodular) and $^{131}$I uptake by lung metastases. Of the 52 DTC patients, 33 patients were female and 19 were male with a male-to-female ratio of 1:1.74. Thirty patients were older than 45 years and 22 patients were less than 45 years, among whom six patients were children. PTC ($n$ = 48) was more than FTC ($n$ = 4). The diagnosis of lung metastases was established after the initial thyroid surgical treatment in 11 patients (21.15%), which we defined as “fine miliaric”. And the other 41 patients (78.85%) were classified into “nodular” before or at the $^{131}$I therapy period with positive imaging results. Among all the cases, seven DTC patients had only lung metastases and 45 cases presented with metastases to other organs, in which 40 (76.92%) had cervical lymph node metastases, five had bone metastases, one had parathyroid metastases. Among 40 patients combined with lymph node involvement after surgery, 18 with lateral cervical lymph node metastases and 22 with bilateral or mediastinal lymph node metastases.

Therapeutic efficacy of $^{131}$I therapy and univariate analysis of factors influencing the serum Tg are shown in Table 2. Significantly decreased serum Tg, which represents the effectiveness of the $^{131}$I therapy, was seen in 30 patients (effective rate, 57.6%). Changes in serum Tg that indicated stabilization and ineffectiveness were both seen in 11 patients (21.2%) after $^{131}$I therapy. Patients with age under 45 years were more likely to respond to serum Tg changes ($P$ = 0.046). But binary logistic regression revealed that none of the six factors, including age at the diagnosis of lung metastases, patient gender, pathological type, local lymph node involvement, size of metastases and $^{131}$I uptake by metastases had statistically significant impacts on the efficacy analysis ($P$ = 0.452, 0.780, 0.444, 0.634, 0.206 and 0.696).

Table 3 shows the results of preablation stimulated Tg. Considering high TgAb levels might influence absolute of Tg, one patient with high TgAb (63%) and one patient who missed the first TgAb were excluded. These 50 patients were classified according to the size of metastases and $^{131}$I uptake by metastases. We defined prognosis as effectiveness and stabilization into “useful”, and ineffectiveness into “useless”. An independent $t$-test shows that the “Fine miliaric” and $^{131}$I uptake positive with great prognosis group was much lower than any other group (all the $P$ < 0.05). And the any other two groups did not have statistical significant.

3. Discussion

Lungs are one of the most frequent distant localization of metastases from DTC. And about 1–4% of DTC patients have lung metastases [11]. $^{131}$I therapy has usually been used for treating these patients. Though a lot of studies reported the different results of efficacy, they all agreed with that the effective rate of $^{131}$I therapy was higher than 50% [14–18]. But it is still controversial. Our results suggest that $^{131}$I therapy administered only on the basis of elevated Tg is effective in 57.6% of patients with about 30 years follow-up, (we did not classify stable cases into good prognosis). Univariate analysis, using $R \times C$ Contingency table, found that age (at the diagnosis of
Table 2
Changes of serum Tg after ^131^I therapy: univariate analysis.

<table>
<thead>
<tr>
<th>Changes of serum Tg</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients eff sta ine X^2</td>
<td>P</td>
</tr>
<tr>
<td>Age at the diagnosis of lung metastases</td>
<td>6.176</td>
</tr>
<tr>
<td>≥ 45</td>
<td>30</td>
</tr>
<tr>
<td>&lt; 45</td>
<td>22</td>
</tr>
<tr>
<td>Gender</td>
<td>2.196</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>33</td>
</tr>
<tr>
<td>Histological type</td>
<td>2.666</td>
</tr>
<tr>
<td>PTC</td>
<td>48</td>
</tr>
<tr>
<td>FTC</td>
<td>4</td>
</tr>
<tr>
<td>Local lymph node involvement</td>
<td>1.897</td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Size of metastases</td>
<td>2.859</td>
</tr>
<tr>
<td>Fine miliaric</td>
<td>11</td>
</tr>
<tr>
<td>Nodular</td>
<td>41</td>
</tr>
<tr>
<td>^131^I uptake by metastases</td>
<td>5.289</td>
</tr>
<tr>
<td>Positive</td>
<td>41</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
</tr>
</tbody>
</table>

* * * P < 0.05.

lung metastases, like most of the studies [16], is different upon the change of Tg within three groups. The younger patients (age < 45 years) have better prognosis than the elderly group. Maybe it is because of shorter duration and lesions were found at an early stage with a better sensitivity of radioiodine than the elder group. Therefore, age can be used as an important indicator for the effect of the ^131^I therapy. The sooner you diagnose and treat with ^131^I for lung metastases from DTC, the better outcome it would have. But in further regression analysis, there were no statistically significant differences between six factors, including age. We consider the reason may be the small cases and we hope to continue to collect more patients’ data in the future. Second, the measure method for Tg and TgAb may have some limits, like manual sampling errors, etc. However, in Table 2, the results of ^131^I uptake (P = 0.071) and the size of metastases (P = 0.239) show more different from other though they have no statistical significance. So further study is still needed.

Tg is a large glycoprotein, which is normally stored in the follicles of the thyroid gland and is closely related to the synthesis and storage of thyroid hormones. The serum Tg levels are frequently used to monitor patients for residual or recurrent disease in follow-up after thyroidectomy and subsequent ^131^I therapy for thyroid cancer [19–21]. As mentioned above, early detection of lung metastasis makes good prognosis. Therefore, finding a reliable tumor marker as soon as possible is very important for DTC lung metastases patients. Physicians could pay more attention to these patients and give them large dose to acquire a better prognosis. Most researchers pointed out that diagnostic whole-body scanning (DxWBS) could reveal the situation of the patients. But it may cause stunning effect. So Yansong Lin [8] focused on the preablation stimulated Tg. They

Table 3
Comparison of preablation stimulated Tg in patients with lung metastases according to classes of size of metastases and ^131^I uptake by metastases.

<table>
<thead>
<tr>
<th>Nodular</th>
<th>Fine miliar</th>
<th>131I uptake positive</th>
<th>131I uptake negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Useless</td>
<td>Useless</td>
<td>Useless</td>
<td>Useless</td>
</tr>
<tr>
<td>Preablation stimulated Tg (mean ± SD)</td>
<td>676.82 ± 10419.4</td>
<td>421.69 ± 466.6</td>
<td>662.94 ± 779.9</td>
</tr>
<tr>
<td>(patients No.)</td>
<td>(17)</td>
<td>(13)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

We defined effectiveness and stabilization as “useful”, and ineffectiveness as “useless”. Null means none of patient in this group.

* * * P < 0.05, comparing with other four different groups using t-test. Last group did not do analysis for just one patient.
reported that it was significantly different between patients with or without distant metastases in 244 DTC patients after total thyroidectomy. The preablation stimulated Tg in metastases group were significantly higher than the no-metastases group. But the preablation stimulated Tg is not recommended, as it can be elevated in most thyroid diseases. This study tried to find out the relationship between preablation stimulated Tg and prognosis. All 52 patients had lung metastases. it was much lower in “Fine miliaric”, 131I uptake positive and “useful” group than any other group. Results are in Table 3. This means that the lower preablation stimulated Tg in patients with lung metastases from DTC, treated by 131I, the better outcome may be accessed.

4. Conclusion

131I therapy is a feasible and effective treatment for DTC lung metastases. A better prognosis may be accomplished in patients who have low level of preablation stimulated Tg.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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