Original article

Lung metastases in patients with differentiated thyroid carcinoma and evaluation of response to radioiodine therapy

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A B S T R A C T

Introduction: The most common site of metastases in differentiated thyroid carcinomas is the lungs. In our study, we aimed to determine the ratios of lung metastases in patients with differentiated thyroid carcinoma and response to radioiodine therapy.

Material and methods: A total of 542 patients with differentiated thyroid carcinoma who were admitted to our clinic were included in the study. High doses of $^{131}$I were administered to the patients with lung metastases. Response to therapy were evaluated with $^{131}$I scans and stimulated serum Tg levels were examined at least 6 months after therapy.

Results: Lung metastases were detected in 17 (3.1%) of 542 patients with differentiated thyroid carcinoma. Of these patients to whom high doses of $^{131}$I therapy were administered, complete response to therapy was obtained in 5 (29.4%), partial response was obtained in 3 (17.6%) and no response could be obtained in 9 (53%) patients.

Conclusion: Although lung metastases from differentiated thyroid carcinomas are rare, those are more common in advanced ages and in males. High doses of $^{131}$I therapy may be partially beneficial in these patients. Thus repetition of therapy is frequently required.

Metástasis pulmonar en pacientes con cáncer diferenciado de tiroides y evaluación de la respuesta a la terapia con radioyodo

R E S U M E N

Introducción: La localización más común de las metástasis a distancia en tumores diferenciados de tiroides es el pulmón. En este estudio se pretende determinar la proporción de metástasis pulmonares en el cáncer diferenciado de tiroides y su respuesta a la terapia con radioyodo.

Material y métodos: Quinientos cuarenta y dos pacientes con cáncer diferenciado de tiroides fueron incluidos en este estudio. Se administraron altas dosis de $^{131}$I a los pacientes con metástasis pulmonares. La respuesta a la terapia se evaluó con estudios con $^{131}$I y niveles de tiroglobulina estimulada al menos 6 meses después de la terapia inicial.

Resultados: Se detectaron metástasis pulmonares en 17 (3,1%) de los 542 pacientes. Tras la terapia con dosis altas de $^{131}$I se observó respuesta completa en 5 (29,4%), respuesta parcial en 3 (17,6%) y no se obtuvo respuesta en 9 (53%) de los pacientes.

Conclusión: Aunque las metástasis pulmonares en los cánceres diferenciados de tiroides son raras, son más frecuentes en edades avanzadas y en varones. Altas dosis de $^{131}$I pueden ser beneficiosas, aunque habitualmente esta terapia debe repetirse.

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Introduction

Thyroid carcinomas are the most common endocrine tumors and yearly incidence has been reported as 7.1–8.8/100,000 in USA. This ratio may vary according to countries. Incidence has been suggested to increase in recent years (approximately 2.4-folds). Differentiated thyroid carcinomas (DTCs) constitute more than 90% of thyroid carcinomas. Although DTC usually has a good prognosis, recurrences and metastases may develop in years. Distant metastases are seen in 10% of papillary thyroid carcinomas and 25% of follicular thyroid carcinomas. Lungs are the most common distant metastases localization followed by bones. Distant metastases in DTCs have been reported to lungs in the ratio 70% and to bones in the ratio of 20%. Lung metastasis is a important factor that effects the prognosis poorly.

Total thyroidectomy, radioiodine ($^{131}$I) therapy and TSH suppression are the most common ways for the treatment of DTCs. Risk of lung metastasis development is about 1.3% in patients who undergo total thyroidectomy followed by radioiodine therapy. Amount of $^{131}$I given in treatment of lung metastases cases should be more than 7.4 GBq (200 mCi) usually. Diffuse (miliary) lung metastases respond better to radioiodine therapy compared to nodular lung metastasis. Ratio of complete response to radioiodine therapy is not very high in DTC cases with lung metastases.
The main complication of radioiodine therapy is pulmonary fibrosis. This complication is rare and especially seen in patients with diffuse lung metastases treated with high doses of $^{131}$I. Limiting total dose and prolonging therapy intervals are recommended in order to prevent this complication.

In our study, we aimed to determine frequency of lung metastases and response to radioiodine therapy in DTC patients who were admitted to our clinic.

**Material and methods**

A total of 542 DTC patients (93 males, 449 females with mean age of $44 \pm 13.5$ years) who are treated and followed up in our clinic and 17 of these patients with lung metastases (4 males, 13 females with mean age of $48.7 \pm 19$ years) were included in the study. Histopathologic diagnosis of 518 patients revealed papillary thyroid carcinoma and for 24 patients it was follicular thyroid carcinoma.

Iodine free diet was applied for at least two weeks prior to $^{131}$I therapy of patients with lung metastases and TSH was kept above $30 \mu U/ml$. Thyroglobulin (Tg) were measured using immunoradiometric analyzer that uses paramagnetic microparticles and chemiluminescent detection technology. Each individual sample was tested a single time for each analyte. Tg results above the manufacturer’s reference limit were considered 0.4–4.1 ng/ml. Therapy doses were determined empirically. It was usually given as 7.4 - 11.1 GBq (200 - 300 mCi) $^{131}$I oral capsules. Number, size, pathological subtype and iodine uptake of metastases were taken into consideration when determining therapy doses. Duration of follow-up was maximum 36 months. Iodine scan was done with 185 MBq (5 mCi) $^{131}$I when TSH > 30 $\mu U/ml$ in patients whose stimulated serum Tg levels < 2 ng/ml six months after therapy. Iodine scan was done with $^{131}$I in therapy doses in patients whose stimulated serum Tg levels > 2 ng/ml six months after therapy. Interval between two therapies was provided to be minimum 6 months in repeated therapies. Therapy was repeated maximum three times. Maximum cumulative dose was 2400 GBq (750 mCi). Patients who responded to therapy completely were classified as Group I, partially responded as Group II and unresponsive ones were classified as Group III. Group I patients whose stimulated serum Tg levels were below 2 ng/ml and iodine scans were negative were accepted to completely respond to therapy (Fig. 1). Group II patients whose iodine scan results were negative or positive but serum Tg levels reduced below initial values although above 2 ng/ml were accepted to partially respond to therapy (Fig. 2). Group III patients whose iodine scan results were negative or positive but serum Tg levels did not change or increase were considered not to respond to therapy (Fig. 3).

**Results**

Of 542 DTC patients included in the study, 518 (95.6%) had papillary cancer and 24 (4.4%) had follicular cancer. Lung metastases were detected in 17 (3.1%) patients. While mean age...
of all patients was 44 ± 13 years, mean age of the patients with lung metastases was 48 ± 19 years. While 449 (82.8%) patients were female, 93 (17.2%) were male; of 17 patients with lung metastases, 13 (76.5%) were female and 4 (23.5%) were male. While the ratio of lung metastases was found as 3.1% among all patients, it was 4.3% in males and 2.9% in females. Lung metastases were seen as 2.5% in patients with papillary cancer and 16.6% in patients with follicular cancer. Clinical and pathologic characteristics of patients are given in Table 1. Lung involvement was diffuse (micronodular) in 5 (29.4%) patients and nodular in 12 (70.6%) patients. Bone metastases were also present in 4 patients with nodular metastases. Lesions did not demonstrate iodine uptake in two patients with nodular lung involvement. No response to therapy could be obtained in these two patients. Complete response to therapy was obtained in 3 (60%) patients with diffuse lung metastases and in 2 (16.6%) patients with nodular lung metastases. In all patients with lung metastases, ratio of complete response to therapy was found as 29.4% (5/17) (Group I), ratio of partial response was found as 17.6% (3/17) (Group II). Ratio of patients who were unresponsive to therapy (33% vs 20%). These data support the fact that prognosis is worse in advanced age and male gender, consistently with literature.

Distant metastases are observed more frequently in follicular type thyroid carcinomas. In our study, lung metastases were detected in 17.4% of follicular carcinoma patients and 2.5% of papillary carcinoma patients. These obtained data are consistent with literature. Of differentiated thyroid carcinoma patients included in our study, 95.6% were found to be papillary type and 4.4% were found to be follicular type. Shah et al., and Ezaki et al. found ratio of papillary carcinoma as 72% and 78% in DTCs in large studies. In our study, ratio of papillary carcinoma was found much higher (95.6%). We consider that this condition arose from putting new pathological classifications into practice in recent years.

Most of the lung metastases seen in DTCs are functional and show iodine uptake. Dedifferentiation is in question in cases that iodine uptake is not observed. This is an indicator of poor prognosis. In our study, 88.2% of lung metastases were seen to be functional. Lung metastases that does not show iodine uptake is the indicator of poor prognosis. Hindie et al. stated that 37% of DTC patients with lung metastases did not show iodine uptake. In our study, iodine uptake was not observed in two patients with nodular lung metastases (11.8%). In these patients, no response was obtained to ¹³¹I therapy. The most reliable detection method for lung metastases is computed tomography (CT). However, especially diffuse lung metastases sometimes cannot be visualized with CT. Ilgan et al. could not make a diagnosis with CT in 18% of patients with lung metastases. We could not observe lung metastases on CT in 29.4% of our patients. Success rate of ¹³¹I therapy is high in lung metastases that are too small to not visualize radiologically. While ten-year survival rate is 90% in patient group with diffuse lung metastases (micrometastases), this ratio was found around 78% in patient group with macro (nodular) metastases that could be diagnosed radiologically. The reason for high success rate in micrometastases may be that preceding distance of ß particles of ¹³¹I is not easy. In the study of Samuel et al., while they obtained complete response to ¹³¹I therapy in 30.8% of DTC patients with ¹³¹I therapy in 30.8% of DTC

### Table 1

Clinical and pathologic characteristics of the patients.

<table>
<thead>
<tr>
<th>Patients with DTC</th>
<th>Mean age</th>
<th>Male</th>
<th>Female</th>
<th>Papillary Ca</th>
<th>Follicular Ca</th>
<th>Bone met.</th>
<th>Nodular lung met</th>
<th>Diffuse lung met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>44 ± 13</td>
<td>542</td>
<td>93</td>
<td>440</td>
<td>518</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with lung metastases</td>
<td>48.7 ± 19</td>
<td>17</td>
<td>4 (23.5%)</td>
<td>17 (76.5%)</td>
<td>13 (76.5%)</td>
<td>4 (23.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of lung metastases</td>
<td>3.1%</td>
<td>–</td>
<td>4.3%</td>
<td>2.9%</td>
<td>2.5%</td>
<td>16.6%</td>
<td></td>
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</tr>
</tbody>
</table>

### Table 2

Clinical and pathologic characteristics of groups with lung metastases.

<table>
<thead>
<tr>
<th>Number (Ratio)</th>
<th>Mean age</th>
<th>Male</th>
<th>Female</th>
<th>Papillary Ca</th>
<th>Follicular Ca</th>
<th>Bone met.</th>
<th>Nodular lung met</th>
<th>Diffuse lung met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I*</td>
<td>41.4 ± 9.8</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II**</td>
<td>46.3 ± 21.3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III***</td>
<td>53.7 ± 20.9</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48.8 ± 19.2</td>
<td>4</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Complete response to therapy.
** Partial response to therapy.
*** No response to therapy.

**Discussion**

DTC is the most common endocrine cancer. Incidence of thyroid cancer has been suggested to increase in recent years. Although DTC is seen frequently, it has the best prognosis in all cancers. Ten-year survival rates are more than 90%,. Age, gender, subtype of the tumor, diameter of the tumor, spread to neighbouring tissues, cervical lymph node involvement, distant metastases and therapy modalities are the main factors affecting prognosis. Lung is the most common site followed by bones for distant metastases. Zettling et al. found ratio of lung metastases as 10% in papillary thyroid carcinoma patients and as 25% in follicular type DTC patients. In our study, these ratios were 2.5% and 17.4%, respectively.

Ratio of lung metastases was lower in our study. We consider that this difference arose from the fact that our study was conducted 9 years later. Because DTC patients are being diagnosed earlier nowadays through advanced medical facilities, thereby metastases ratios may be found lower. Advanced age and male gender are the leading risk factors for lung metastases. In our study, mean age of patients with lung metastases was found to be higher than that of all patients, consistently with literature (all patients 44 ± 13; patients with lung metastases: 48.7 ± 19). Mean age of the patients who did not respond to therapy was higher than the patients who responded the therapy (53.7 ± 20.9 vs 41.4 ± 9.8). Ratio of males was observed to be higher in the group who did not respond to therapy compared to the group who responded to therapy (33% vs 20%). These data support the fact that prognosis is worse in advanced age and male gender, consistently with literature.
patients with lung metastases, ratio of partial response was 65.4% and no response was 3.8%. In the study of Schlumberger et al. conducted with 394 DTC patients with lung and/or bone metastases, they stated that there was iodine uptake in two thirds of metastases and those responded to therapy in the ratio of 46%. We could obtain complete response to therapy in 29.4% of our patients and partial response to therapy in 17.6%, we could not obtain response to therapy in 53%. Ratio of patients who did not respond to therapy may seem high however some of these patients could be administered one or two doses of 131I therapy. Reduction of this ratio with repeated therapies is strongly possible.

In conclusion, lung metastases in DTC patients are seen more frequently in advanced ages and males. Achieving complete treatment in lung metastases is not easy. Iodine uptake of metastases (functional metastases) is the most important factor determining the success of therapy. Metastases’ being too small to not to visualize radiologically (micrometastases-diffuse) and patients’ being young are the two other factors determining the success of therapy. That repeated therapies may be beneficial in patients whereas the first therapy was not successful should be kept in mind.

Conflict of interest

The authors have no conflict of interest to declare.

References