Management and Prognosis of Metastases to the Thyroid Gland

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BACKGROUND: Intrathyroid metastases (ITM) of extrathyroid cancer are rare and have a poor prognosis. The aim of this work was to identify the sites of primary cancers and the treatment and prognosis of these lesions.

STUDY DESIGN: This retrospective study was carried out on patients treated between 1982 and 2002 in the surgical departments of the University hospitals of Poitiers, Limoges, Tours, and Nantes, France. All diagnoses were confirmed by cytology or histologic examination.

RESULTS: Twenty-nine patients (41 to 78 years) had ITM. Primary cancers were renal cell in 16 patients, lung in 4, digestive in 4, sarcoma in 1, melanoma in 1, neuroendocrine in 1, and of unknown origin in 1 patient. For 10 patients, diagnoses of primary cancer and ITM were synchronous. For 19 patients, delay between diagnosis of the primary cancer and ITM was 6.8 years (2 months to 16 years). Diagnosis was confirmed with fine-needle aspiration 3 times and with histologic examination of the thyroid 26 times. Twenty-seven patients had thyroidectomy; two were not operated on. After treatment of ITM, 13 patients had new metastatic sites. Mean followup for all patients was 2.3 years. Seven patients (24%) (6 with renal cancer) were disease free (followup 4.5 years). Four patients were alive with disease (followup 1.4 years). Eighteen patients (62%) died of their disease at a mean delay of 1.4 years.

CONCLUSIONS: ITM are rare but the diagnosis should be borne in mind when patients have a history of cancer (mainly renal cancer). Preoperative diagnosis and complete evaluation could avoid unnecessary thyroidectomy because numerous patients had diffuse metastases. (J Am Coll Surg 2005;200: 203–207. © 2005 by the American College of Surgeons)
analyzed included: patients’ age and gender, clinical presentation of the ITM, location of primary cancer, time from the initial cancer diagnosis to appearance of metastasis, location and number of synchronous or metachronous metastases, and treatment and course of the disease after diagnosis of ITM. Information concerning followup was obtained by written questionnaire or direct communication with the physicians or the patient.

StatView 5.0 was used for statistical analysis of data. Survival curves were drawn according to the Kaplan-Meier method. Comparison of overall survival was performed with the log-rank tests. Statistical significance was set at a threshold of \( p < 0.05 \).

RESULTS

Twenty-nine patients were included in this series: 15 women and 14 men, with a mean age of 62 years (range 41 to 78 years). Revealing symptoms were a multinodular goiter in 17 patients (2 had unilateral recurrent nerve palsy), a thyroid nodule in 8, and a cervical lymph node in 1 (data unknown for 1 patient). Four patients had a tracheal compression. All patients but one had normal thyroid function. One patient had hyperthyroidism. Five patients had fine-needle aspiration cytology (FNAC). In three patients, FNAC led to diagnosis of ITM. In two patients, it was nonconclusive.

The primary cancers are shown in Figure 1. Renal cancers were all clear cell cancers. Digestive cancers included two colonic cancers, one adenocarcinoma of the cardia, and one epidermoid carcinoma of the esophagus. The sarcoma was a leiomyosarcoma of the forearm. This patient had had a lower left pulmonary lobectomy for a metastasis 2 years before the ITM. Diagnoses of primary and thyroid localizations were synchronous in 10 patients (34.5%). For these patients, primary cancers were four lung cancers, two digestive cancers, one renal cancer, one melanoma, one neuroendocrine tumor, and the cancer of unknown origin. In six of these patients, the ITM revealed the cancer (three lung, one renal, one neuroendocrine, and one digestive). Three of the four other patients (with synchronous ITM) had tracheal compression. The patient with unknown primary cancer had been operated on for a brain lesion, which was a secondary tumor. Postoperatively, CT scan revealed a thyroid lesion. One of these four patients, without cervical compression, had FNAC that led to diagnosis. All four of these patients had clinical examination, cervical ultrasonography, and CT scan. Thyroid locations were metachronous in 19 patients (65.5%). They appeared with a mean delay of 6.8 years (2 months to 16 years) after diagnosis of the primary cancer. Delayed appearance of the ITM in patients with renal cancer (excluding the patient with synchronous ITM) was 7.6 years (2 months to 16 years). For nonrenal cancer, the mean delay for metachronous ITM was 3.1 years (1 to 5 years).

Twenty-one patients had total thyroidectomy and six isthmolobectomy (one of whom had a unilateral recurrent nerve resection because of a massive infiltration). Seven of the patients had lymph node resection because of the presence of cervical lymphadenopathies (six of those treated by total thyroidectomy and one treated by isthmolobectomy). Two patients had frozen section during operation. In one patient, diagnosis was clear cell tumor; in the other patient, an intrathyroid parathyroid adenoma was suspected. In both patients, it was an ITM of renal origin on definitive examination. Total thyroidectomy was performed because of massive infiltration: a presence of nodule in the opposite lobe. In six patients the reason was unknown. Two patients were not operated on because they had other distant metastases and had a preoperative diagnosis by FNAC. One was treated with chemotherapy (adenocarcinoma of the cardia) and the other did not receive treatment (lung carcinoma and synchronous ITM). Five patients had postoperative cervical radiotherapy associated with one session of chemo-
therapy (patient suffering from a sarcoma). Two patients had adjuvant chemotherapy after thyroid intervention.

Histologic examination of the thyroids of the 27 patients who were operated on showed 9 patients with massive thyroid infiltration: 4 unilateral and 5 bilateral. The primary tumors of the thyroid infiltrations were three digestive cancers, two melanomas, one lung, one neuroendocrine, one unknown origin, and one kidney. In 10 patients, there was a solitary metastatic nodule and 6 had multiple metastatic nodules (data unknown for 2 patients). All patients who had lymph node resection had involved nodes. One patient also had a 5-mm papillary cancer. The 16 histologic examinations of primary renal cancers were compared with thyroid lesion and thyroglobulin immunostaining was performed. It was negative. These lesions were not clear cell primary thyroid cancer.

After diagnosis of ITM (within 1 month), a complete evaluation was performed in all patients. Eight patients had other metastatic sites: five had pulmonary metastases, four hepatic metastases, three bone metastases, and two adrenal metastases. The primary sites of these cancers were two lung, two melanomas, and one each in the colon, kidney, and neuroendocrine, and one of unknown origin.

Mean followup was 2.3 years (range 3 months to 9 years) after diagnosis of ITM. During this followup, 13 patients developed new metastases. The primary cancers, treatments of ITM, metastatic sites, time from the initial cancer diagnosis to the metastasis, and outcomes for these patients are shown in Table 1.

Actuarial patient survival as determined by Kaplan-Meier analysis for all patients is shown in Figure 2. Difference in survival between patients with primary renal cancers and the others is shown in Figure 3. This difference was statistically significant (p < 0.0001). At the end of our study, 7 patients (24%) were alive and disease free (6 renal cancers and the sarcoma) after 4.5 years (range 1 to 9 years). Four patients (14%) were alive with a progressive lesion after 1.4 years (range 2 to 30 months). And, finally, 18 patients (62%) have died at a mean delay of 1.4 years (range 1 month to 8 years) after diagnosis of ITM. Patients who died of an extrarenal cancer all survived for less than 1 year. Among the 16

<table>
<thead>
<tr>
<th>Primary cancer</th>
<th>Treatment of ITM</th>
<th>Location</th>
<th>Delay*</th>
<th>Outcomes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Lobectomy</td>
<td>Pleura</td>
<td>2 y</td>
<td>Dead (3 y)</td>
</tr>
<tr>
<td>Kidney</td>
<td>TT</td>
<td>Parotid, pancreas</td>
<td>1 y</td>
<td>Alive with tumor (2.5 y)</td>
</tr>
<tr>
<td>Kidney</td>
<td>TT</td>
<td>Kidney</td>
<td>1 y</td>
<td>Dead (3 y)</td>
</tr>
<tr>
<td>Kidney</td>
<td>TT</td>
<td>Bone</td>
<td>2 y</td>
<td>Dead (4 y)</td>
</tr>
<tr>
<td>Kidney</td>
<td>TT</td>
<td>Liver, pancreas</td>
<td>3 y</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>TT</td>
<td>Pancreas, kidney</td>
<td>5 y</td>
<td>Dead (8 y)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lobectomy</td>
<td>Pancreas</td>
<td>2 y</td>
<td>Dead (2.2 y)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>TT, Chemotherapy</td>
<td>Bone</td>
<td>3 mo</td>
<td>Dead (4 mo)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>TT</td>
<td>Skin</td>
<td>1 mo</td>
<td>Dead (2 mo)</td>
</tr>
<tr>
<td>Cardia</td>
<td>Chemotherapy</td>
<td>Mediastinal nodes</td>
<td>3 mo</td>
<td>Dead (4 mo)</td>
</tr>
<tr>
<td>Colon</td>
<td>TT, LND</td>
<td>Adrenal gland</td>
<td>2 mo</td>
<td>Dead (4 mo)</td>
</tr>
<tr>
<td>Lung</td>
<td>Lobectomy, LND</td>
<td>Brain</td>
<td>2 y</td>
<td>Alive with tumor (2.2 y)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>TT</td>
<td>Bone</td>
<td>2 mo</td>
<td>Dead (10 mo)</td>
</tr>
<tr>
<td>Unknown</td>
<td>TT, LND</td>
<td>Bone</td>
<td>2 mo</td>
<td>Dead (3 mo)</td>
</tr>
</tbody>
</table>

ITM, intrathyroid metastases; LND, lymph node dissection; TT, total thyroidectomy.
* ITM—new metastases.
† Followup since diagnosis of ITM.

Figure 2. Actuarial survival for all patients.
patients presenting a renal cancer, 7 died after a mean delay of 3.3 years (range 3 months to 8 years) and 9 (56%) were alive (recurrence free for 6 patients) after a delay of 3.7 years (3 months to 9 years). Among the 8 patients who had ITM associated with other metastatic sites, 7 died (mean delay 6 months, range 2 to 16 months) and the only surviving patient had a progressive tumor and a short followup (3 months). Among the 21 patients who had isolated ITM, 11 were deceased (mean delay 2.1 years, range 2 months to 8 years), 7 were alive without tumor, and 3 were alive with tumor.

DISCUSSION
In our series, as described in the literature, clear cell renal cancer is the most commonly found (55%) primary site with ITM.1,4,5,8 Other primary cancers were mainly lung, digestive, and melanoma. Unlike other authors, we did not observe any ITMs in patients with breast cancer.1,3,8 The site of the primary cancer is not always localized, despite all the radiologic examinations.1,3 Numerous primary cancers were reported in the literature: colon, parotid gland, gastric leiomyosarcoma or adenocarcinoma, esophagus, liver, uterus, uterine cervix, pancreas, bladder, liposarcoma, and Merkel cell carcinoma.1,5,14-19 In six of our patients, the ITM revealed the primary cancer. This has already been noted for cancers of the kidney, liver, and lungs.5,7,16,20 In Heffess and colleagues’7 series based on 36 ITMs of renal cancer, it revealed the primary cancer in one-third of patients.

The mode of revelation of the ITMs in our series was no different from a primary thyroid disease: multinodular goiter, thyroid nodule, cervical lymph node, or recurrent nerve palsy. Preoperative distinction between a primary versus a secondary thyroid neoplasm is almost impossible.7 These nodules appear as inhomogeneous, hypoechoic mass on ultrasound. The true metastatic nature of the tumor is recognized only after tumor sampling. Aspiration cytology was carried out in only five patients, and three of these led to a diagnosis. Its great interest was to avoid unnecessary thyroidectomy in two patients with poor prognosis. If this examination had been performed systematically, we would certainly have avoided operating on other patients with numerous metastases at the time of thyroidectomy. The small number of FNAC carried out is because this series took place over a period of 20 years, and FNAC was less widely practiced in the past. Noncontributory FNAC can result from interpretation difficulties (particularly if the primary cancer is unknown) or from the fact that the puncture concerned a colloidal nodule of multinodular goiter. Another potential source of confusion in cytologic interpretation is the difficulty of distinguishing primary anaplastic thyroid carcinoma from metastatic high-grade malignancy. Positive immunostaining for thyroglobulin suggests a primary thyroid malignancy.7 Currently, we think that aspiration cytology should be performed in cases of thyroid nodules, particularly in patients with a history of cancer.

Not all of our patients had total thyroidectomy despite the recommendations of some authors.3 Histologic examinations showed that, with the exception of massive infiltrations of thyroid tissue, the nodular metastasis was solitary in 10 patients out of 16. We think that total thyroidectomy is only advisable where bilateral nodules are present on preoperative ultrasonography. A lymphadenectomy was carried out on seven patients. It was only performed for cases of preoperative macroscopic lymph node involvement, which explains the fact that all these patients had involved nodes. Because of the small number of lymphadenectomies performed, we cannot draw any conclusions about the mode of dissemination (hematogenic or lymphatic) to explain the ITMs. In the literature, the hematogenic pathway is the more commonly cited.3

In cases of renal cancers, we observed very long delays between diagnosis of the primary tumor and that of the ITM (mean delay 7.6 years), as has already been reported: 9.4 years for Heffess and colleagues2 and 1 to 26 years for Nakhjavani and colleagues.1 Long disease-free intervals have also been described for breast and
uterine adenocarcinomas. There is no explanation for this long latent period between the identification of the primary cancer and the development of clinical thyroid metastasis.

In our series, 62% of patients died and only 24% were alive without evidence of disease. The prognosis depends essentially on the primary cancer and the isolated nature of the ITM. Patients with renal cancer had a better prognosis than others (see Fig. 3). Their mortality rate is lower and the survival time of the deceased patients is greater than that of patients presenting an extrarenal cancer. Patients presenting a nodular ITM also had a better prognosis than those who had a thyroid infiltration, but the primary cancers of the latter were eight times out of nine nonrenal cancers. The patient presenting with sarcoma on the forearm was the only recurrence-free survivor with an extrarenal tumor.

These results indicate that surgical intervention should mainly be performed on patients with renal cancer after establishing the solitary nature of the ITM, or at least that the other metastases can be removed. When the ITM affects patients with extrarenal primary cancer, widespread examinations should be carried out. It is very often a polymetastatic disease. For polymetastatic disease, thyroid operation should only be performed in patients presenting signs of tracheal compression. FNAC is an essential tool to improve preoperative diagnosis of thyroid nodule.

Author Contributions

Study conception and design: Mirallié, Kraimps
Acquisition of data: Mirallié, Rigaud, Mathonnet, Gibelin, Regenet, Hamy, Bretagnol, de Calan, Le Néel
Analysis and interpretation of data: Mirallié, Rigaud, Mathonnet, Kraimps
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Supervision: Kraimps

REFERENCES