Metastatic Renal Cell Carcinoma to the Thyroid Gland
A Clinicopathologic Study of 36 Cases

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BACKGROUND. Clear cell tumors of the thyroid gland in general are uncommon. Metastatic renal cell carcinoma (RCC) to the thyroid gland is a rare occurrence but must be considered in the differential diagnosis of a thyroid gland clear cell neoplasm to prevent misclassification, potentially resulting in inappropriate clinical management.

METHODS. Thirty-six cases of metastatic RCC to the thyroid were retrospectively retrieved from the files of the Endocrine Registry of the Armed Forces Institute of Pathology.

RESULTS. The tumors occurred in 22 women and 14 men, ages 53–80 years (mean, 64.9 years). Symptoms were present for a mean of 13.0 months. The tumors generally affected a single lobe of the thyroid gland as a solitary mass (n = 30; 83%), measuring 1.0–15.0 cm in diameter (mean, 3.8 cm). Histologically, the tumors were composed of polygonal cells with clear cytoplasm, distinct cell membranes, and small compact eccentric nuclei within a rich vascular network. Diastase-sensitive, periodic acid-Schiff-positive material (n = 22; 61%) and/or Oil Red O-positive material (n = 5; 14%) were noted. Thyroglobulin immunohistochemistry was negative in the foci of metastatic RCC. Although the majority of the patients had documented previous evidence of an RCC (n = 23; 64%) as remotely as 21.8 years before the thyroid metastases (mean, 9.4 years), the metastatic tumor to the thyroid gland was the initial manifestation of RCC in 13 patients. The majority of patients (n = 23; 64%) died with disseminated disease (mean, 4.9 years), but 13 patients (36%) were alive or had died without evidence of disease (mean, 9.1 years).

CONCLUSIONS. In the presence of a clear cell tumor of the thyroid gland, the diagnostic considerations must include metastatic RCC. The light microscopic features may suggest this possibility and the diagnosis can be established by supplemental histochemical and immunohistochemical studies. Surgical treatment of the metastatic disease is suggested, as this may result in prolonged patient survival. Cancer 2002;95:1869–78.

KEYWORDS: thyroid gland, renal cell carcinoma, metastatic disease, immunohistochemistry, surgery, prognosis.

A metastatic neoplasm to the thyroid gland identified during life is a distinctly uncommon cause of thyroid enlargement. Usually, metastases are found at autopsy as part of widespread disease or they directly invade the thyroid gland from a neoplasm from adjacent organs such as the neck and/or mediastinum. Although secondary involvement of the thyroid gland by renal cell carcinoma (RCC) is rare, it is still one of the more common neoplasms to metastasize to the thyroid gland (< 0.1%).1–8 When present, metastatic RCC can mimic primary thyroid gland neoplasms, potentially leading to diag-
nostic difficulties. This diagnostic dilemma is further complicated by several factors. These include its presence as a solitary mass in the thyroid gland (most often a solitary mass lesion of the thyroid gland is representative of a primary thyroid lesion) and its occurrence in patients with no known history of an RCC (i.e., occult primary neoplasm) with the metastatic deposits in the thyroid gland representing the initial manifestation of their renal disease.

We undertook this study to underscore the importance of the preoperative diagnosis of metastatic RCC to the thyroid gland. We attempt to define the histologic criteria for the recognition of metastatic RCC, as well as the utilization of adjunct histochemical and immunohistochemical stains in the diagnosis. In addition, we discuss the differential diagnosis of clear cell neoplasms of the thyroid gland and provide insight into the appropriate clinical management of metastatic RCC to the thyroid gland.

MATERIALS AND METHODS

Thirty-six cases of metastatic RCC to the thyroid gland were identified in the files of the Endocrine Registry at the Armed Forces Institute of Pathology from 1959 to 1998. These cases were identified in a review of 37,158 (0.1%) benign and malignant thyroid neoplasms seen in consultation between 1959 and 1998. Secondary clear cell tumors resulting from direct invasion from malignant tumors of the contiguous organs were omitted from consideration, as were cases of systemic disease (e.g., lymphoma). The cases included in this study were obtained from civilian sources, including university medical centers and foreign contributors, military hospitals, and Veterans Administration medical centers.

Patient demographics, clinical symptoms at presentation, and past medical and surgical history (specifically, a history of RCC or renal surgery) were reviewed for all patients. In addition, we reviewed radiographic, surgical pathology, and operative reports. We also obtained information from oncology data services by written questionnaires or direct communication with the physician(s) or patient. Follow-up data, available for all patients, included information regarding tumor location, treatment modalities, and current patient and disease status. With the exception of one case in which there was only radiologic evidence of a neoplasm involving the kidney, all cases included in this study have histologic confirmation of RCC. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

All cases had hematoxylin and eosin-stained slides for morphologic assessment of metastatic RCC. Periodic acid-Schiff (PAS) stain (with and without diastase digestion), Mayer’s mucicarmine stain, and the Oil Red O procedure were performed. Immunophenotypic analysis was performed on a single block in 32 cases with suitable material, according to the standardized avidin-biotin method of Hsu et al.9 on 4-μm thick, formalin-fixed, paraffin-embedded sections. Commercially available immunohistochemical antibodies for cytokeratin (AE1/AE3/LP34: AE1/AE3, mouse monoclonal antibody [MoAb], 1:200, Dako, Carpinteria, CA; LP34, mouse MoAb, 1:40, Boehringer Mannheim Biochemicals, Indianapolis, IN) and thyroglobulin (mouse MoAb, 1:600, Dako) were used. Pre-digestion was performed for 3 minutes with 0.05% Protease VIII (Sigma, St. Louis, MO) in a 0.1 M phosphate buffer, pH 7.8, at 37 °C. Appropriate standard positive and negative (serum) controls were used throughout. The lesional cells were graded as reactive or nonreactive.

RESULTS

Clinical Demographics and Presentation

There were 22 women and 14 men, ages 53–80 years (mean, 64.9 years) at the time of clinically apparent thyroid lesions (Table 1). The mean age at presentation for women and men was 67.5 and 60.8 years, respectively, although this difference was not statistically significant. We separated the patients into two groups based on the type of presentation: RCC as the initial presentation (Group 1) and the thyroid tumor as the initial presentation (Group 2). There were 23 patients in Group 1 and 13 patients in Group 2. There was an overwhelming female predominance (11:2 female-to-male ratio) in Group 2, a finding similar to thyroid gland disorders in general. However, when there was a known history of RCC, there was no difference in the gender distribution (11 women and 12 men). There was no appreciable difference in the mean age at presentation between Groups 1 and 2, the location of the primary RCC, or the overall tumor size (Table 1).

All patients experienced enlargement of the thyroid gland (mass lesion), often with associated symptoms related to mass effect, such as hoarseness (compression of the recurrent laryngeal nerve), difficulty breathing, difficulty swallowing, and/or pain (n = 8). Thirty patients presented with a solitary nodule in the thyroid gland, three patients presented with multifocal or bilateral disease, and three patients were noted to have a mass of the thyroid during routine physical examination for other reasons. The symptoms were present from 2 weeks to 10 years, with an overall
average of 13.0 months. The patients with a known RCC had a shorter mean duration of symptoms (8.3 months) than patients without a known primary tumor (21.0 months). This difference may be related to more frequent physical examinations and radiographic studies for patients with a known primary RCC tumor as part of their follow-up. Furthermore, the overall longer mean duration of symptoms for patients without a known primary tumor may be related to the generally nonspecific nature of the initial presenting symptoms (e.g., slow enlargement of the thyroid gland), which often were managed symptomatically without a specific diagnostic evaluation. Even though a few patients had a long history of goiter (n = 4), a change in size or symptoms prompted clinical attention. There was no clinical evidence of thyroid dysfunction (i.e., hypothyroidism or hyperthyroidism).

**Clinical Management and Outcome**

The thyroid masses were all managed by surgery, irrespective of the treatment for the primary RCC (a few patients had been treated with radiation therapy for the primary RCC). The treatment included a lobectomy in 21 patients and a total thyroidectomy in 15 patients. In all of our patients, the thyroid mass was an isolated clinical finding at the time of presentation, even though other metastatic foci developed during the follow-up period. Follow-up information was available for all patients (Table 2). All patients had clear cell RCC, without any primary chromophobe or papillary RCC. Thirteen patients were either alive (n = 8) or had died (n = 5) without evidence of disease (mean, 9.8 years), whereas 23 patients had died with widely disseminated disease (mean, 4.9 years). These results yielded an overall raw 5-year survival rate of 51.4% and a raw 10-year survival rate of 25.7%. Because thyroid metastases were already present, an RCC disease-free survival rate is not applicable.

To simplify the follow-up data, the patients were grouped according to previous evidence of RCC as described above (Table 2). Furthermore, survival from the date of the diagnosis of RCC also is presented (Table 2).

**Thyroid tumor as initial presentation**

In 13 patients (2 men and 11 women), the thyroid mass (enlargement) was the initial manifestation of the disease. In these patients, the diagnosis of a clear cell RCC prompted a clinical and radiographic investigation. A nephrectomy was performed between 4 and 554 days after the diagnosis of a metastatic clear

| TABLE 1 |
|---|---|---|
| Clinical Features of Metastatic Renal Cell Carcinomas to the Thyroid Gland | All cases | Renal cell carcinoma as primary presentation | Thyroid tumor as primary presentation |
| All | 36 | 23 | 13 |
| Gender | | | |
| Women | 22 | 11 | 11 |
| Men | 14 | 12 | 2 |
| Mean age at presentation (yrs) | | | |
| All | 64.9 | 65.3 | 64.2 |
| Women | 67.5 | 69.2 | 65.9 |
| Men | 60.8 | 61.8 | 54.5 |
| Length of symptoms (mos) | | | |
| Range | 0.5–120 | 0.5–52 | 0.5–120 |
| Mean | 13.0 | 8.3 | 21.0 |
| Type of presentation | | | |
| Solitary mass | 30 | 19 | 11 |
| Multifocal masses | 3 | 3 | 0 |
| Mass, not further specified | 3 | 1 | 2 |
| Anatomic location | | | |
| Right | 19 | 13 | 6 |
| Left | 11 | 6 | 5 |
| Bilateral | 3 | 3 | 0 |
| Unknown | 3 | 1 | 2 |
| Tumor size (cm) | | | |
| Range | 1.0–15 | 1.0–15.0 | 1.5–4.5 |
| Mean | 3.8 | 4.1 | 3.2 |
cell RCC to the thyroid in 11 of these patients. One patient refused surgery and the primary RCC was discovered in another patient at autopsy 1 year after metastatic disease was diagnosed. One patient is alive without evidence of disease at 4.9 years, two died without evidence of disease (9.6 and 11.9 years, respectively), and 10 patients died with widely disseminated disease an average of 4.3 years after the thyroid mass was diagnosed. These figures are slightly lower if the survival from the date of diagnosis of the RCC is calculated (Table 2).

**RCC as initial presentation, but with subsequent thyroid enlargement**

Of the 23 patients with a known RCC, 22 had a previous nephrectomy for RCC from 2 to 21.9 years before the development of the thyroid gland metastases (mean, 9.4 years). One patient had a clinically palpable mass, confirmed by radiographic images. Of these patients, seven are alive without evidence of disease (mean, 6.4 years after the thyroid presentation) and three had died without evidence of disease (mean, 15.5 years after the thyroid presentation). The remaining 13 patients died with widely disseminated disease an average of 5.4 years after the thyroid mass was diagnosed. The overall survival from the date of RCC diagnosis was much longer, as would be expected, with a mean survival of 14.9, 21.0, and 16.5 years, respectively. At the time of death for the patients with widely disseminated disease, the other metastatic foci included the vertebrae, lymph nodes, liver, lung, pleura, brain, bones, and adrenal glands.

**Pathology**

**Macroscopic findings**

The masses in the thyroid gland specimens were well circumscribed, encapsulated (contained within adenomatoid nodules that, by definition, do not have a capsule), and varied from 1.0 cm to 15.0 cm in greatest diameter (mean, 3.8 cm). The masses in the thyroid gland in patients in whom the thyroid gland lesion was the initial presentation of the RCC were on average smaller (mean, 3.2 cm) than the masses in patients with a known primary RCC (mean, 4.1 cm). The numbers were too few to perform a meaningful statistical analysis. The tumors were solitary masses in 30 patients and multifocal and/or bilateral in 3 patients. This information was unavailable for three patients. The tumors involved the right lobe \( (n = 19) \) more frequently than the left lobe \( (n = 11) \), but this difference was not meaningful and did not relate to the side of the primary RCC. It is noteworthy that none of the patients in whom the thyroid mass was the initial presentation of the RCC had multifocal and/or bilateral disease.

On sectioning, the tumors appeared lobulated, well demarcated, and sharply circumscribed or encapsulated, from soft to partially necrotic and bright yellow to reddish-tan (Fig. 1). The primary RCC affected the left kidney in 20 patients, the right kidney in 8 patients. The particular side was unknown for eight patients. The information was unavailable for three patients. The tumors involved the right lobe \( (n = 19) \) more frequently than the left lobe \( (n = 11) \), but this difference was not meaningful and did not relate to the side of the primary RCC. It is noteworthy that none of the patients in whom the thyroid mass was the initial presentation of the RCC had multifocal and/or bilateral disease.

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**Microscopic findings**

The metastatic foci were usually encapsulated \( (n = 19) \) cases). However, in many cases, the deposits of met-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Patient outcome</th>
<th>A, NED</th>
<th>D, NED</th>
<th>D, D</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>8</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Survival range from date of thyroid presentation</td>
<td>0.9–16.5</td>
<td>9.6–20.2</td>
<td>0.3–18.8</td>
</tr>
<tr>
<td>Survival mean from date of thyroid presentation</td>
<td>5.4</td>
<td>13.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Years between primary and thyroid presentation (mean)</td>
<td>7.2</td>
<td>3.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Survival from date of RCC diagnosis (mean)</td>
<td>13.7</td>
<td>18.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Thyroid tumor as initial presentation</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Range</td>
<td>n/a</td>
<td>9.6–11.9</td>
<td>0.4–11.2</td>
</tr>
<tr>
<td>Mean</td>
<td>4.9</td>
<td>10.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Survival from date of RCC diagnosis (mean)</td>
<td>4.8</td>
<td>10.4</td>
<td>4.0</td>
</tr>
<tr>
<td>RCC as initial presentation</td>
<td>7</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Range</td>
<td>0.9–16.5</td>
<td>13.1–20.2</td>
<td>0.3–18.8</td>
</tr>
<tr>
<td>Mean</td>
<td>6.4</td>
<td>15.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Years between primary and thyroid presentation (mean)</td>
<td>8.4</td>
<td>5.5</td>
<td>10.9</td>
</tr>
<tr>
<td>Survival from date of RCC diagnosis (mean)</td>
<td>14.9</td>
<td>21.0</td>
<td>16.5</td>
</tr>
</tbody>
</table>

A, NED: alive, no evidence of disease; D, NED: dead, no evidence of disease; D, D: dead with disseminated disease; RCC: renal cell carcinoma.
Metastatic RCC were found within adenomatoid nodules \((n = 10)\), which are not by definition encapsulated or within follicular adenomas \((n = 4; \text{Figs. 2, 3})\). Although well circumscribed in the majority, the cells were occasionally identified infiltrating the capsule and invading small to medium vessels, making them virtually indistinguishable from follicular thyroid carcinomas. The predominant histologic pattern was characterized by the presence of small nests and cords of neoplastic cells separated by a prominent vascular stroma (Fig. 4). A primary thyroid follicular epithelial tumor was simulated by a “pseudofollicular” architectural arrangement in nine cases in which cystic spaces were lined by clear cells and filled with erythrocytes. Furthermore, a tubular, angiomatoid, and a papillary pattern as a minor component were present in two cases each, respectively. The neoplastic deposits were composed of polygonal or elongated cells with clear cytoplasm, distinct cytoplasmic membranes, and small, compact eccentric nuclei (Fig. 4). Nuclear pleomorphism was minimal to nonexistent. The cytomorphologic features of thyroid papillary carcinoma, including nuclear enlargement, irregularities in nuclear size and shape, dispersed to optically clear appearing nuclear chromatin, crowding or overlapping nuclei, nuclear grooves, and nuclear inclusions, were not identified in any of these foci. Although clear cell features were the dominant finding in all cases, foci of cells with slightly eosinophilic cytoplasm were present in eight cases. Hemorrhage \((n = 6)\), a lymphoid infiltrate \((n = 6)\), fibrosis \((n = 2)\), microcysts \((n = 2)\), microcalcifications \((n = 2)\), and necrosis \((n = 1)\) were also noted. The background thyroid parenchyma harbored lymphocytic thyroiditis \((n = 5)\) and microscopic papillary carcinoma \((n = 2)\).

In the majority of the cases in which a capsule was present, the neoplastic cells were identified infiltrating the capsule with invasion of small to medium vessels. This feature coupled with the histologic similarities to
thyroid follicular epithelial tumors easily led to a diagnosis of thyroid follicular carcinoma.

**Special procedures**
The metastatic foci contained variable amounts of diastase-sensitive, PAS-positive material, which was indicative of glycogen in the cytoplasm of the clear cells (Fig. 5). The intensity varied from weak to strong, ranging from patchy \((n = 15)\) to diffuse \((n = 7)\) in distribution. The PAS-positive material was only graded when identified within the cell cytoplasm in the neoplastic deposits, as the PAS reaction is also used to accentuate colloid in the central luminal space of thyroid follicular epithelial cells. No stainable mucin was demonstrated in the neoplastic cells in any of the cases evaluated. In a few cases with available material \((n = 5)\), numerous droplets of neutral fat (Oil Red O stain) were demonstrated in the neoplastic cells, not in the thyroid follicular cells.

All metastatic foci were nonreactive with thyroglobulin. There were some difficulties in interpretation, especially in cases lying within or juxtaposed to thyroid follicular epithelial cells. The thyroglobulin staining in these cells was often very faint and non-granular, representing diffusion rather than true immunoreactivity. As expected, diffuse and strong keratin immunoreactivity was demonstrated in both the metastatic and thyroid follicular cells. However, there was a slight difference in the pattern of reactivity, with an accentuation along the membranes in the metastatic RCC cells, whereas a cytoplasmic reaction was seen in the residual thyroid follicular epithelium.

**DISCUSSION**
Metastasis to the thyroid gland is an uncommon occurrence. However, autopsy results show that 1.9–22.4% of patients with generalized malignancies have metastasis to the thyroid gland.\(^{10}\) The clinical and histomorphologic features of most metastatic tumors to the thyroid gland (reported in autopsy series) are sufficiently distinctive to achieve separation without any difficulty on the part of the clinician or pathologist. According to one large autopsy series, malignant melanoma (39%) and breast carcinoma (21%) account for the largest number of tumors metastasizing to the thyroid gland as part of widely disseminated disease (excluding lymphoma and leukemia).\(^{5}\)

Although the incidence of metastatic disease to the thyroid gland in autopsy series is variable and is compounded by the lack of systematic examination of the thyroid gland during autopsy,\(^{11}\) antemortem manifestations of metastatic disease are rare.\(^{8,12-14}\) The scarcity of antemortem evidence of metastatic disease probably is related to the nonspecific nature of the symptoms. Clinical presentation of a mass lesion in the thyroid gland that proves to be metastatic disease is distinctly uncommon, with only a few cases of malignant melanoma, breast carcinoma, and lung carcinoma identified in the files of the Armed Forces Institute of Pathology or reported in the literature.\(^{12}\) However, when a thyroid mass presents as the clinical manifestation of metastatic disease, RCC seems to be the most frequent tumor type. In the absence of a clinical history, the sudden enlargement of the thyroid gland in an otherwise healthy patient makes the diag-
nosis of metastatic disease challenging. This is compounded further by histologic similarities between metastatic deposits and primary thyroid lesions.

RCCs are neoplasms of adulthood that are seen most frequently in the sixth decade of life with a male predominance. However, because thyroid diseases in general are more frequent in women, the predominance of female patients in this series is acceptable. The average age of our patients at presentation of RCC (57.4 years, excluding the patients in whom the thyroid mass was the initial manifestation of the RCC) was similar to the findings reported in the literature. RCC is known for its capacity to behave in an unpredictable and unusual fashion. Metastatic foci from RCC usually develop in the lower respiratory tract, skeletal system, lymph nodes, brain, liver, and skin, with other sites (such as the thyroid gland) described less frequently. The recognition of metastatic foci is important clinically because metastases usually suggest a poor prognosis, with the exception of a few tumors, such as RCC. It is peculiar that RCCs develop late and/or as a solitary metastasis. Although metastatic foci are present in about 25% of RCCs at the time of the diagnosis of the primary malignancy (synchronous), metastatic disease can develop as part of the latency of the tumor with delayed development of metastases after many years of dormancy (metachronous). This is especially true if the primary carcinoma is clinically a low-stage malignancy. Moreover, a solitary metastasis from RCC occurs with an incidence rate of about 1–4%, of which about 1% occurs in the thyroid gland. There are many tumors in the peripheral circulation, although only a few form metastases. The presence of a solitary RCC metastasis suggests the ability of the host to destroy the majority of the circulating neoplastic cells.

The thyroid gland is one of the most vascularized organs in the body and one would expect it to be the site of metastatic disease. It has been suggested that the thyroid gland, when altered by goiter, neoplasms, or thyroiditis, is more vulnerable to metastatic growth due to metabolic changes with a decrease in oxygen and iodine content. Beahrs et al. postulated that the rich vascular supply inhibits the entrapment of tumor emboli. However, when degeneration occurs in neoplasms or in adenomatoid nodules, metastatic neoplastic cells are readily deposited as a consequence of the interrupted blood supply. In support of this theory, adenomatoid nodules or adenomas were identified in this series in 10 patients, whereas chronic thyroiditis was noted in five patients. Therefore, 42% of patients in this series had abnormal thyroid glands (as a caveat, additional abnormalities may have been present in the remaining gland but not included in the sections available for examination).

In contrast to this theory, others have suggested that vascular deterioration by itself would not be sufficient to account for metastatic disease, that the filtering system of the lungs would probably remove most tumor emboli, and that there was no difference in frequency of metastasis in altered thyroid glands versus normal thyroid glands. Whichever theory may be correct, there is no explanation for the long latent period between the identification of the primary tumor (for the patients with a known renal primary) and the development of clinical thyroid gland metastases (mean, 9.4 years in this clinical study).

Metastatic RCC may be the first manifestation of the disease, even masquerading as a primary thyroid gland neoplasm. In the setting of a solitary thyroid mass many years after nephrectomy in a patient with a long disease-free interval (arbitrarily defined as > 10 years), the recognition that it may be an RCC may pose a diagnostic problem not only for the pathologist but also for the clinician. The absence of symptoms related to the urinary tract in many cases and sometimes a failure to obtain a detailed clinical history may lead to an equivocal or incorrect diagnosis when the patient first presents with a thyroid gland mass.

In none of the patients in our series was the RCC discovered simultaneously with the metastatic thyroid tumor. Given the nature of our consultation service, the history of RCC usually was disclosed within a few days of rendering the diagnosis. It is noteworthy that in 13 of our cases (36.1%), the metastatic focus was the initial presentation of the RCC. However, on average, the metastatic focus developed 9.4 years after the initial nephrectomy (range, 2 months to 21.9 years). In fact, nine patients in this clinical series presented 10 years or more after the initial nephrectomy, reinforcing the need for long-term clinical follow-up of patients with RCC.

Surgical treatment of patients with solitary thyroid gland metastases is recommended because of the unusually good prognosis of our patients and of patients reported in the literature when they were treated with definitive surgical therapy. A number of factors may be associated with a favorable prognosis after resection of the metastases, including 1) a long interval between the primary tumor resection and the development of the metastatic focus (often in excess of 10 years as identified in this clinical series), 2) evidence of a solitary or isolated lesion in the thyroid gland without evidence of widespread metastases, 3) spontaneous regression of metastatic lesions, 4) demonstration of extensive necrosis in the resected specimen, and 5) slow evolution or growth of the tumor and a lack of
clinical symptoms. Moreover, spontaneous remission or regression of cancer metastases is uncommon, but has been well described in RCC and especially in RCC metastatic to the lung. None of the patients in our series had a spontaneous regression, but all had surgery within a short time of documenting metastatic disease rather than only being followed clinically.

The mean survival rate reported in the literature is variable and limited to case reports or small series with a short follow-up period, making the analysis unreliable for purposes of predicting survival. It has been suggested that in the setting of solitary RCC metastasis of any anatomic site, the 5-year survival rate from the date of the nephrectomy ranges between 30% and 70%, which is much higher than the approximately 5% 5-year survival rate when widespread disease is present. In our series, the 5-year survival rate from the date of nephrectomy was 80% and the 10-year survival rate was 66%. In fact, the mean overall survival period from the date of the nephrectomy was 12.3 years (range, 0.2–31.5 years), with a 6.4-year mean overall survival from the date of the thyroid metastasis (range, 0.3–20.2 years). Therefore, there is an overall excellent prognosis for RCC patients with solitary metastasis (disease stage was not reported for the original material), further highlighting the necessity for surgical resection of solitary metastatic foci to the thyroid gland to assure the possibility of a favorable clinical outcome.

The preoperative distinction between a primary versus a secondary thyroid neoplasm is almost impossible. Radiographic differences cannot be used to discriminate between primary or metastatic tumor as both of these lesions will appear as “cold” nodules on radioiodine uptake studies or as an “inhomogeneous, hypoechoic” mass on ultrasound. Therefore, radiographic imaging is not helpful in differentiating a primary thyroid neoplasm from a metastasis to the thyroid gland. The true metastatic nature of the tumor is recognized only after tumor sampling with pathologic assessment as there is no clinical pattern associated with metastatic lesions that differentiate it from a primary thyroid cancer. Therefore, all patients for whom there is clinical or radiographic evidence of a mass (particularly in solitary masses) in the thyroid gland require a fine-needle aspiration biopsy or a core-needle biopsy of the mass, irrespective of whether the patient has a known history of a previous malignancy (RCC or another tumor type) or no known primary malignancy elsewhere. If the patient is known to have a previous malignancy of renal origin, then the suspicious radiographic lesion should be surgically excised rather than have the patient undergo a biopsy of the lesion. This would allow for an accurate diagnosis with initiation of proper treatment, thereby potentially increasing long-term patient survival. The challenge of making the diagnosis of a metastatic clear cell RCC in the thyroid gland on intraoperative consultation (i.e., frozen section) is difficult due to fixation artifact that makes the cytoplasm appear more eosinophilic than clear in appearance. However, architectural features, such as the presence of fibrovascular cores and erythrocytes within the pseudofollicles, may assist in making an accurate distinction between a primary tumor and metastatic RCC. However, in practicality, this is a very challenging differential diagnosis at intraoperative consultation. RCCs and thyroid follicular epithelial neoplasms with clear cells may have a variety of histologic patterns that make a distinction on morphologic grounds alone difficult. RCCs may have pseudofollicles filled with blood. The cells have clear cytoplasm, distinct boundaries, and small, compact, dark nuclei. Thyroid follicular epithelial tumors with clear cells are rare and include follicular adenoma, follicular carcinoma, and papillary carcinoma. The clear cell component within a primary thyroid follicular neoplasm may be the dominant cell type or may represent a minor component of the entire neoplastic proliferation (Fig. 6). The presence of clear cells in any thyroid follicular neoplasm does not alter the overall prognosis of that particular tumor type. The presence of large amounts of glycogen (diastase sensitive, PAS positive), large amounts of lipids, and the absence of mucin favor the diagnosis of RCC. In contrast, thyroid tumors with clear cells do not have intracytoplasmic glycogen, although moderate amounts are seen occasionally. It is important to emphasize that colloid droplets always stain with PAS, but are diastase resistant. Variable amounts of neutral fat (Oil Red O technique) are seen in lipid-rich thyroid primary tumors, which are virtually indistinguishable from RCCs. Studies on lipid-rich thyroid follicular lesions have shown that
scattered neutral lipid droplets occur intracellularly and their accumulation represents a degenerative phenomenon that increases with age. Therefore, when a lipid-rich thyroid primary neoplasm is suspected, additional special studies are needed to assist in rendering the diagnosis. The majority of RCCs are keratin and epithelial membrane antigen immunoreactive, whereas they are nonreactive with thyroglobulin and thyroid transcription factor-1 (TTF-1). Primary thyroid follicular epithelial tumors are also immunoreactive with keratin, but stain strongly and diffusely with thyroglobulin and TTF-1. These antigenic profiles allow for accurate and reliable separation of RCCs from primary thyroid follicular epithelial neoplasms.

In summary, the identification of a clear cell tumor of the thyroid gland must be evaluated to exclude the possibility of metastatic RCC. This is especially true when it is found in a patient with a previous history of RCC, irrespective of the temporal sequence from the previous RCC. Although the clinical manifestations and radiographic findings are often nonspecific, the architectural, cytologic, histologic, histochemical, and immunohistochemical features are sufficiently distinctive to allow differentiation of a primary thyroid follicular epithelial neoplasm from RCC. It is important to distinguish between a primary thyroid follicular epithelial neoplasm and metastatic RCC to correctly manage the patient, especially in the presence of an occult RCC. The course of RCC is unpredictable and the thyroid lesion may represent the only manifestation of the disease. Surgical treatment of the solitary metastatic deposit is recommended as the patient may enjoy a prolonged survival. Surgery is even more beneficial if the RCC was known before the metastasis, as determined in this clinical series.

**REFERENCES**


