CASE REPORT PEER REVIEWED | OPEN ACCESS

Thyroid metastasis 21 years after radical nephrectomy: A case report and review of literature

Israr Khan, Shatha Alhilaly, Ramy Elbaz

ABSTRACT

Introduction: The thyroid gland is a highly vascular organ, yet it is an uncommon site for metastasis. Clear cell renal carcinoma is the most frequent site of origin of thyroid metastases and represents 12% to 34% of all secondary thyroid tumors, but cases presenting more than 10 years after nephrectomy are exceedingly rare. This report aims to present a case of 21-year renal cell carcinoma (RCC) with thyroid metastasis in a 60 year old patient who was treated with thyroidectomy and systemic therapy and review the existing literature.

Case Report: A 60-year-old female presented with dysphagia and a neck mass 21 years following radical nephrectomy. She was treated with partial thyroidectomy and pathology came to show metastatic RCC with positive safety margin.

Conclusion: Metastasis to the thyroid should be considered in any patient with a history of malignancy, especially RCC, even decades after initial treatment. Fine needle aspiration is a crucial diagnostic tool, but immunohistochemical staining is often necessary for a definitive diagnosis.

Keywords: Delayed metastasis, Renal cell carcinoma, Thyroid tumor

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Received: 10 October 2025
Accepted: 10 December 2025
Published: 21 January 2026

How to cite this article

Khan I, Alhilaly S, Elbaz R. Thyroid metastasis 21 years after radical nephrectomy: A case report and review of literature. J Case Rep Images Urol 2026;11(1):1–5.

Article ID: 100059Z15IK2026

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doi: 10.5348/100059Z15IK2026CR

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all adult malignancies [1]. It is known for its unpredictable and often late pattern of metastasis. It is observed that extremely delayed distant metastasis that occurs in other organs including the lung, bone, and liver 10 years after nephrectomy for RCC is not rare, with a prevalence of 4.7% to 11% [2]. While the thyroid gland is highly vascular, making it a potential site for hematogenous spread, it is an uncommon site for metastatic disease, representing <5% of all thyroid malignancies [3–5]. Renal cell carcinoma is, however, a common source of metastasis to the thyroid. Most metastases occur within the first five years of diagnosis, but there are rare reports of "extremely delayed" metastasis presenting more than 10 years after nephrectomy [6]. This phenomenon poses a significant diagnostic challenge, as a new thyroid nodule in a patient with a remote history of cancer is often presumed to be a primary thyroid tumor. We present a rare case of solitary thyroid metastasis from RCC which appeared 21 years after radical nephrectomy.

CASE REPORT

A 69-year-old female has a history of left radical nephrectomy in 1994 for a 7.8 cm clear cell RCC (CcRCC), staged as pT2aN0M0 according to the AJCC TNM staging system. The patient had been on regular follow-up after

radical nephrectomy and last CT chest abdomen and pelvis was done in September 2014, and it was free. The patient has medical history of hypertension (HTN), type II diabetes mellitus (DM), coronary artery bypass grafting surgery (CABG) for coronary artery disease in 2012 and total abdominal hysterectomy for multiple leiomyomas in 1992. In October 2015, she presented with an air way compression discovered during an upper gastrointestinal endoscopy for persistent dysphagia for six months. Computed tomography (CT) chest and neck revealed large thyroid nodule (Figures 1 and 2). Fine needle aspiration (FNA) was done. However, the cytology was inconclusive. Partial thyroidectomy was done and surprisingly revealed clear cell renal cell carcinoma with positive safety margin (Figure 3). The pathology was confirmed by immunohistochemical staining. The tumor was positive for PAX-8, CD10, and EMA, and were negative for Thyroglobulin and TTF-1 which are known to be specific tumor for primary thyroid cancers. The patient's postoperative course was uneventful apart from mild seroma around the thyroid bed which was managed conservatively. Uro-oncology multidisciplinary (MDT) meeting was held in November 2015 to discuss the possibility of complete thyroidectomy in view of positive

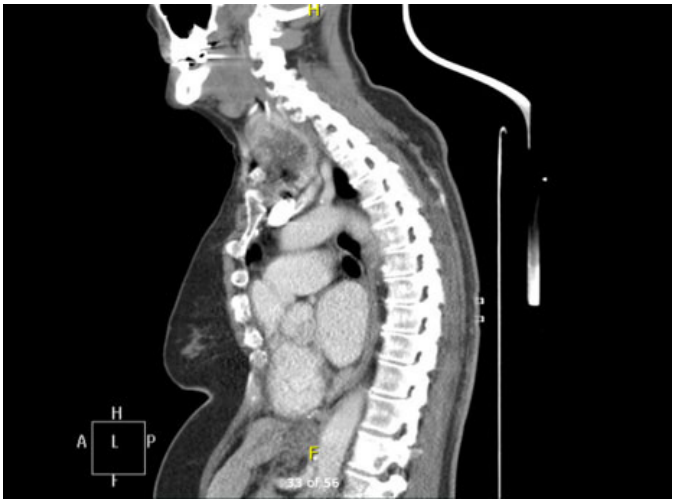

Figure 1: CT chest sagittal view showing thyroid mass.

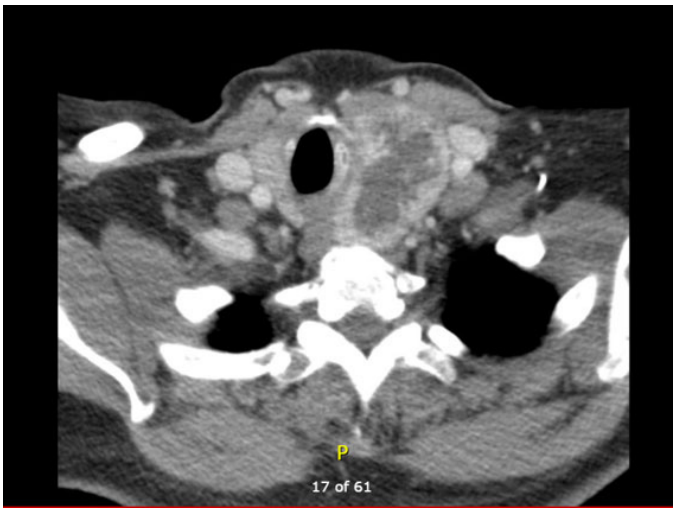

Figure 2: CT chest axial view showing thyroid mass.

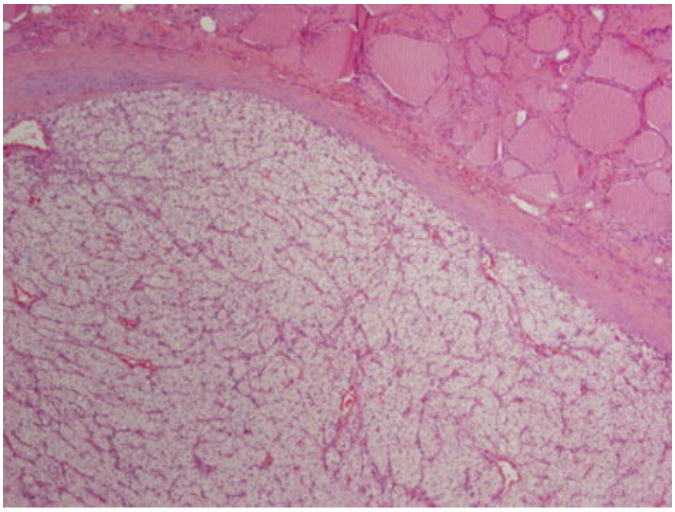

Figure 3: Hematoxylin–eosin-stained specimen showing the normal thyroid and atypical cells with abundant clear cytoplasm and central nucleus.

safety margin or going directly to systemic therapy, and new positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) scans were requested in December 2015. However, bilateral lung and T12 metastases were revealed. Radiotherapy was given for T12 lesion and immune checkpoint inhibitor, Pazopanib with denosumab and levothyroxine were commenced. The treatment was monitored over the next two years with frequent echocardiograms, blood pressure monitoring, liver and cardiac function tests. Last PET-CT scan was in November 2017, and it was stable regarding lung metastases and T12 lesion. In March 2018, the patient died of sudden myocardial infarction.

DISCUSSION

The occurrence of CcRCC recurrence following nephrectomy varies greatly, with metastases appearing anywhere from a few months to several years following the original diagnosis [7, 8]. Two to three percent of thyroid cancers are metastases [3–5] with skin, breast, lung, kidney, and head and neck tumors being the most prevalent original tumors. Metastatic thyroid lesions are frequently hidden, as evidenced by the increased percentage of secondary thyroid gland cancers discovered in autopsy investigations, which range from 5% to 24% [9].

Because of its abundant blood supply, some authors have proposed that the thyroid is a common site of metastasis. They also suggested that goiter, neoplasms, or thyroiditis would make the thyroid gland more vulnerable to metastatic growth because of metabolic changes, including decreases in the amount of oxygen and iodine in the gland [10]. However, according to some writers, the frequency of metastasis in changed thyroid glands is the same as that in normal thyroid glands [10].

About 12–34% of all secondary thyroid cancers are CcRCC metastases to the thyroid gland [9]. Metastatic thyroid tumors might be a synchronous or metachronous metastasis of an existing CcRCC, or they can be the initial sign of CcRCC [3]. Metastases typically manifest as metachronous lesions, frequently occurring years following nephrectomy. Possible factors suggesting the slow development of thyroid metastases are the filter activity of lungs, the high concentration of oxygen and iodine in the thyroid, and the local cytoregulating effect of the thyroid hormones [11]. According to Boles and Cerny [12], it is the Batson's venous plexus between the vertebral and epidural venous system that facilitates this spread. These venous systems are valveless and offer an easy way for metastatic cells to spread with low resistance. Increase in intra-abdominal and thoracic pressure causes retrograde flow in these veins; cancerous kidney cells can bypass the pulmonary capillary filtration and metastasizes in the head and neck. This pathogenetic suggestion has been recently reproposed by Kancherla et al. [13, 14]. As in this instance, a primary thyroid tumor may first be mistaken for metastatic CcRCC.

In large literature reviews of 111 cases of thyroid metastases after radical nephrectomy, intervals from nephrectomy to the diagnosis of thyroid metastasis and localization of metastases were evaluated. Time interval was successfully specified for 87 patients (30 men, 47 women, and 10 of unknown gender). In 79 individuals (90.8%), thyroid metastases were metachronous, while in eight cases (9.2%), they were synchronous. The sex differences between synchronous (four men, four women) and metachronous (26 men, 43 women) metastases were not statistically significant ($p = 0.769$, $p = 0.086$). Men (8.7 ± 6.4 years [range: 1.0–19.5]) and women (8.8 ± 5.9 years [range: 0.25–26.3]) did not significantly differ in the time between nephrectomy and thyroid metastasis diagnosis. Regarding thyroid Metastases Localization, 78 individuals (77%) presented with a single nodule and 23 patients (23%) with multiple nodules, when known (n = 101). Metastatic thyroid multiple nodules ranged from two to three in each lobe when specified (4/23 cases). Most thyroid metastases (37% and 34%) were found in the right and left lobes, respectively with the remaining 29% having thyroid metastases in either the isthmus or both thyroid lobes. In this review, the primary pathology for all cases was clear cell renal cell carcinoma (CcRCC) except in 3 cases where the primary tumor was carcinoid, papillary, and chromophobe RCC [14].

Two prognostic factors for thyroid metastases in patients with RCC have been identified: (A) presence of an isolated metastasis and (B) treatment. Prolonged survival was reported in patients with solitary thyroid metastases [15]. Kierney et al. [16] reported 1, 3, and 5-year disease-free survivals of 77%, 59%, and 31%, respectively, for treated patients compared with a 36%, 17%, and 1.7% rate for patients with untreated metastases from a historical series.

It is challenging to distinguish between primary and secondary tumors prior to surgery, even though individuals with a history of renal malignancies may be at risk for CcRCC metastases to the thyroid gland. Both patients present comparable radiological characteristics, with the nodule appearing "cold" on radioiodine uptake studies and as a hypoechoic, non-homogeneous, and vascularized mass on ultrasound examination [17]. Fine needle aspiration cytology of the lesion can aid in preoperative diagnosis, indicating a secondary neoplasm; nevertheless, cytological features are frequent in both primary and secondary neoplasms, and a metastatic tumor can easily be misdiagnosed as a primary tumor [18].

To the best of our knowledge, our case has the longest interval from nephrectomy time until occurrence of thyroid metastasis. Like most authors, we avoid doing a core biopsy in cases when the cytological results are unclear. Therefore, histological analysis following thyroidectomy is used to diagnose metastatic CcRCC. Pathologists should suspect a secondary thyroid tumor based on the patient's clinical history of previous cancers, multifocal growth pattern, sinusoidal pattern of vascularization, and clear cell appearance of the cytoplasm. With metastatic cells of CcRCC negative for thyroglobulin, calcitonin, and TTF-1 and positive for CD10 and vimentin, immunohistochemistry can be useful for differential diagnosis [10, 18]. However, a new thyroid mass is more likely to be a primary than a secondary tumor, even in patients who have had prior CcRCC.

Thyroidectomies are recommended for patients with no further metastases; their prognosis is good. However, the prognosis for patients with widespread disease is poor, and the removal of the thyroid should only be done to alleviate compressive symptoms. In patients who cannot be thyroidectomized, methods to prolong survival include medical therapy, immunotherapy (e.g., interferon-α), multikinase inhibitors (sunitinib, sorafenib, axitinib, pazopanib), anti-vascular endothelial growth factor agents (bevacizumab), and mammalian target of rapamycin inhibitors (temsirolimus, everolimus).

Although our case happened in 2018, it has been reported only now because it required retrospective review of the patient's records to ensure the accuracy and completeness of the clinical details. We believe the case still provides valuable learning points despite the time gap.

CONCLUSION

Patients with a positive history for CcRCC and a thyroid nodule should be evaluated for thyroid metastases. It is challenging to distinguish between primary and secondary cancers prior to surgery. Patients with suspected nodules and metastatic cells that test positive for CD10 and vimentin but negative for thyroglobulin, calcitonin, and TTF-1 can be evaluated

with immunohistochemistry. A thyroidectomy is required if the metastases are limited to the thyroid gland.

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Acknowledgments
The authors would like to express their sincere gratitude to The Urology Department, Scunthorpe General Hospital, Northern Lincolnshire and Goole NHS Foundation Trust for facilitating clinical data collection. Also, they would like to thank the patient's son for his agreeing to participate in the study.

Author Contributions

Israr Khan – Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shatha Alhilaly – Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ramy Elbaz – Conception of the work, Design of the work, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None.

Consent Statement
Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.