Clinical Case Report

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Multiple metastases of clear-cell renal cell carcinoma to different region of the nasal cavity and paranasal sinus 3 times successively

A case report and literature review

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Abstract

Rationale: Distant metastasis of clear-cell renal cell carcinoma (ccRCC) to the nasal cavity and paranasal sinus is rare. Endoscopic biopsy used to be performed for diagnosis when it is difficult for complete resection due to intense bleeding during surgery. According to previous literature, the outcomes of metastasis after endoscopic surgery remain unclear.

Patient concerns: A 62-year-old man with a history of epistaxis was referred to our institution. The clinical, computed tomography (CT) and magnetic resonance imaging (MRI) examination indicate metastasis to sinonasal sinuses.

Diagnoses: He was histopathologically diagnosed with different anatomical structures of nasal cavity and paranasal sinus metastases 6, 14, and 15 years after the initial nephrectomy for ccRCC.

Interventions: He underwent endoscopic surgery 3 times, once at the time of each metastasis.

Outcomes: He survived for 20 years despite of multitransfers and died due to multiple organ failure.

Lessons: Metastasis of ccRCC to the nasal cavity and paranasal sinus is characterized by varied growth rates, metastatic times and spreading patterns; ccRCC metastasis should be considered with the presence of hemorrhagic lesions in the nasal cavity and paranasal sinus. Endoscopic surgery is the first-line treatment.

Abbreviations: ccRCC = clear-cell renal cell carcinoma, CT = computed tomography, DCE-MRI = dynamic contrast-enhanced MRI, HIF= hypoxia inducible factor, IGS = imaging guidance system, MOF = multiple organ failure, MRI = magnetic resonance imaging, NCCN = National Association Cancer Network, PFS = progression-free survival, PLRA = prelacrimal recess approach, RCC = renal cell carcinoma, T1WI = T1 weighted imaging, TIC = time-intensity curve, VEGF = vascular endothelial growth factor.

Keywords: clear-cell renal cell carcinoma, endoscopic surgery, epistaxis, metastasis, nasal cavity, paranasal sinuses

1. Introduction

Renal cell carcinoma (RCC) is the most common malignant tumor that metastasizes to the nasal cavity and paranasal sinus. It is divided into 16 subclasses, of which clear-cell renal cell carcinoma (ccRCC) (85%) is most common,[1] exhibiting varied growth rates, metastatic time, and spreading patterns.[2] Approximately 25% of ccRCC patients demonstrate distant metastasis at the first diagnosis, while 20% to 50% of metastases occur several years after primary tumor surgery.[3] The most common sites are the lungs (76%), local lymph nodes (66%), bone (42%), and liver (41%).[3] Additionally, 15% of metastases occur in the head and neck,[4] with approximately 1% transferring to the head and neck in the absence of other metastases,[2] and rare cases involve transfer to the nasal cavity and paranasal sinus. This report presents one case of ccRCC that metastasized 3 times to the nasal cavity and paranasal sinus after nephrectomy.

2. Case report

A 62-year-old man with a history of recurrent right-side epistaxis was referred to our institution on January 14, 1997. The patient's medical history was significant for left nephrectomy 6 years earlier. Upon nasal endoscopy, a purple red mass arising from the right middle meatus was noted. Computed tomography (CT) of the nose and paranasal sinuses revealed a mass in the right ethmoid and sphenoid sinus, with bone resorption of the superior wall of the sphenoid sinus (Fig. 1A). Upon magnetic resonance imaging (MRI), the lesion appeared isointense according to T1 weighted imaging (T1WI), with strong enhancement, suggesting a hypervascular sinonasal tumor in the right ethmoid sinus

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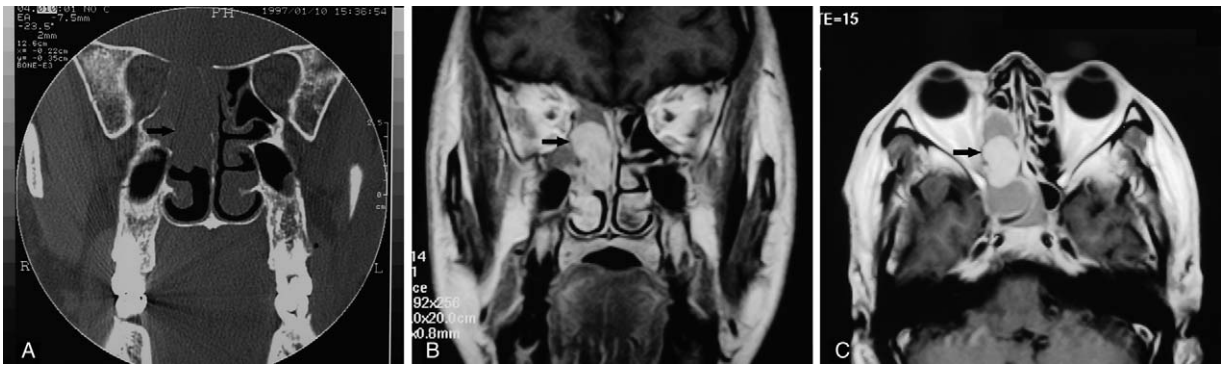

Figure 1. (A–C) ccRCC metastasizes to the right ethmoid sinus. (A) Coronal computed tomography (CT) of nose and paranasal sinuses reveals a mass in the right ethmoid and sphenoid sinus, with bone resorption of the superior wall of the sphenoid sinus. (B) Coronal magnetic resonance imaging (MRI) of the nose and paranasal sinuses shows a strong, enhanced lesion with a clear boundary. (C) Axial MRI demonstrates a hypervascular sinonasal tumor at the right ethmoid sinus. ccRCC = clear-cell renal cell carcinoma, CT = computed tomography, MRI = magnetic resonance imaging.

(Fig. 1B and C). Complete endoscopic removal of the right sinonasal tumor was performed on January 17, 1997. A well-defined tumor was observed, based on the right posterior ethmoid, with mucus in the sphenoid sinus and part of the root dura exposed. Histological examination of the specimen confirmed metastatic ccRCC of renal origin (Fig. 2A and B). The patient was admitted to our hospital again on October 8, 2005, complaining of bloody nasal discharge. Endoscopic examination showed a reddish, fragile, hemorrhagic mass on the left olfactory cleft measuring 1 cm in diameter, as well as atresia of the right sphenoid sinus (Fig. 3A). Paranasal sinus CT depicted soft tissue in the left nasal cavity and right sphenoid sinus (Fig. 3C). MRI suggested a lesion located in the left olfactory cleft and a mucous cyst in the right (Fig. 3B and D). The patient underwent endoscopic surgery. A mass originated from the root of the left superior nasal turbinate, adhering to the nasal septum. Endoscopic resection was performed with a negative margin, and atresia of the right sphenoid sinus was opened, enlarged and filling with mucus; smooth mucosa was noted. The pathology report attributed the tumor in the left olfactory cleft to metastatic ccRCC with negative margins. The patient presented to our department for a lesion in the right maxillary sinus that was noticed in a physical examination before initial presentation on September 8, 2006. There was no positive finding by nasal endoscopy. MRI showed a tumor located in the anterior and lateral walls of the right maxillary sinus with a clear boundary (Fig. 4A and B). En bloc resection was performed endoscopically via prelacrimal recess approach (PLRA) to better expose the lesion in the maxillary sinus. A smooth easily movable mass with distinct edges was noted at the bottom of the maxillary sinus (Fig. 4C and D). The pathology was consistent with metastatic ccRCC.

The patient metastasized to the left lung and left renal pedicle in 2001 and the inferior lobe of left lung in March 2007; these metastases were treated with surgery. Later, multitransfer to the bilateral lung, left chest subcutaneous, right kidney, retroperitoneal lymph nodes and pancreas occurred in September 2008, and the right hip bone in December 2009, with symptomatic treatment. Follow-up to 20 years after the first nephrectomy showed no new metastasis or recurrence in the nasal cavity and paranasal sinus, and the patient died of multiple organ failure (MOF) due to advanced tumor consumption.

3. Discussion

Metastases to the nasal cavity and paranasal sinus are rarely found; RCC is the most common primary tumor (49%), followed by malignancies in the lung, urogenital ridge, breast, and gastrointestinal tract.[4,5]

RCC consists of a histopathologically diverse group of solid tumors, accounting for approximately 0.3% of all malignant tumors, 3% of adult malignancies, and 90% of all renal

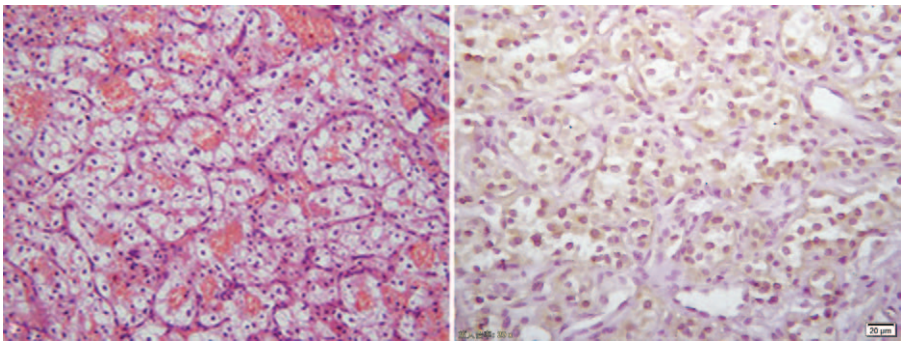

Figure 2. (A and B) Pathology and immunohistochemistry of ccRCC metastasis to the nasal cavity and paranasal sinus. (A) Hematoxylin and eosin (HE) staining shows clear cell borders, eosinophilic cytoplasm, round or oval nuclei, and tumor cells arranged in nests with capillaries in between (HE × 200). (B) Immunohistochemical staining reveals CD10 positivity (SP × 200). ccRCC = clear-cell renal cell carcinoma, HE = hematoxylin and eosin, SP = streptavidin-perosidase.

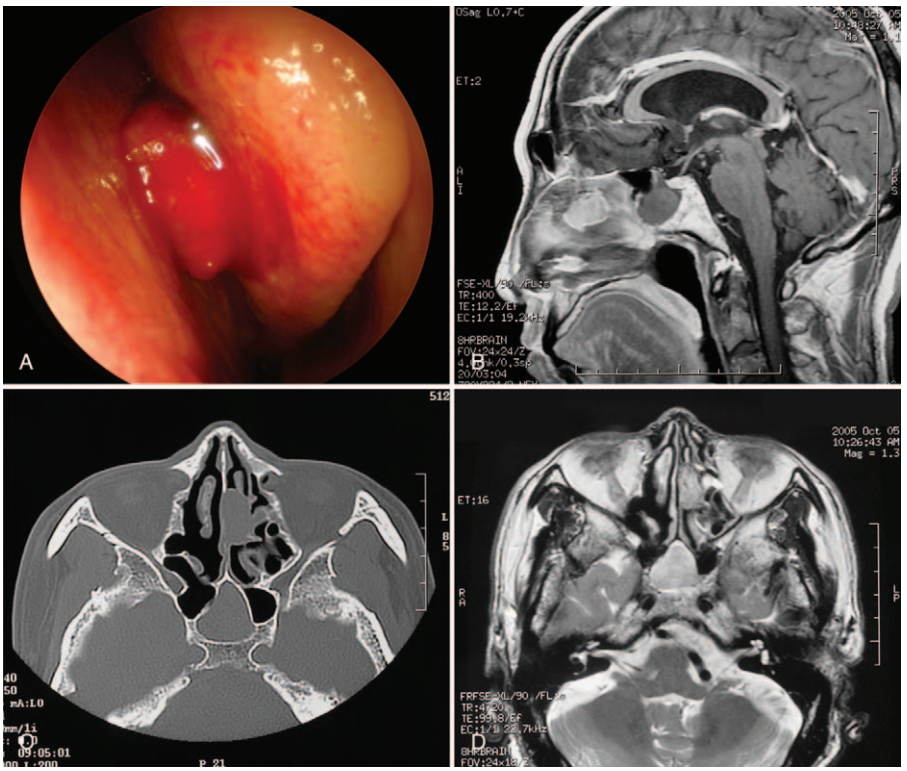

Figure 3. (A–D) ccRCC metastasis to the left olfactory cleft. (A) Endoscopic examination shows a reddish, fragile, hemorrhagic mass on the left olfactory cleft, 1 cm in diameter, and atresia of the right sphenoid sinus. (B) Sagittal MRI of the nasal cavity and paranasal sinus shows a lesion in the left olfactory cleft with a clear, smooth border and heterogeneous density in an enhanced scan, as well as a mucous cyst in the right sphenoid sinus. (C) Axial CT suggests a mass with homogeneous density in both the left olfactory cleft and the right sphenoid sinus. (D) Axial MRI depicts a lesion with a mixed signal based on T2-weighted imaging (T2WI) in the left olfactory cleft and a high-signal lesion in the right sphenoid sinus, with a clear boundary. ccRCC = clear-cell renal cell carcinoma, MRI = magnetic resonance imaging.

malignancies. It is generally observed in patients of 30 to 60 years old,[6] especially in males,[7] with a male–female ratio of approximately 1.5:1.[2] According to the 2016 WHO Classification of Tumours of the Urinary System, RCC comprises 16 subtypes with varied prognoses. The most common is ccRCC (85%).[1] The clinical behavior of ccRCC is unpredictable in terms of its growth rate, the timing of metastasis and the variability of metastatic spreading patterns.[2] Prognoses are worse than those for papillary renal cell carcinoma and chromophobe renal cell carcinoma but better than those for collecting duct carcinoma and renal medullary carcinoma.[8] The aim of this report is to describe a rare case of ccRCC that metastasized to different nasal cavity and paranasal sinus sites, followed by a review of the relevant literature.

Reports differ regarding the metastatic time and spreading patterns of ccRCC. Approximately 25% of patients have distant metastases upon the first diagnosis, while 20% to 50% of patients experience metastasis years after curing with primary surgery.[3] McNichols et al[9] performed a study of 506 patients with RCC and found that 11% metastasized 10 years after nephrectomy and one case 31 years after primary cancer resection. The most common sites are the lungs (76%), local lymph nodes (66%), bone (42%), and liver (41%);[3] approximately 15% of patients demonstrate head and neck metastases,[4] while only 1% experience head and neck metastases in the absence of other sites.[2] The most common locations in the head and neck are the nasal cavity and paranasal sinus, throat, oropharynx, temporal bone, thyroid and parotid gland, in that order.[4] Alvarez-Mugica et al[10] reported one case of transfer to the nasal cavity and paranasal sinus 17 years after nephrectomy. The presented case metastasized to the ethmoid sinus, left lung, left renal pedicle, olfactory cleft, inferior lobe of the left lung, maxillary sinus, bilateral lung, left chest subcutaneous, right kidney, retroperitoneal lymph nodes, pancreas, and hip bone, successively. The patient had metastasis to the ethmoid sinus, olfactory cleft, and maxillary sinus 6, 14 and 15 years, respectively, after the initial surgery. The metastatic time and spreading pattern were unpredictable, and the locations were confirmed as new metastases, not recurrences. At present, this is the first such clinical report in the world.

Based on a review of 28 cases, including 27 cases in 20 reports from 1982 to 2017 and the present case and excluding 5 cases without details on metastatic sites, the most common metastatic sites are the nasal cavity (8 cases, 34.8%), ethmoid sinus (8 cases, 34.8%), and maxillary sinus (8 cases, 34.8%). Cases have also demonstrated metastasis to the frontal sinus, sphenoid sinus, orbital, and nasopharynx.[4–7,11] Individuals may also experience transfer to the nasal septum, pterygopalatine fossa, and nasal tip[5,12] (Table 1). Endoscopic biopsy is used for diagnosis when it is difficult to perform complete resection due to intense bleeding during surgery.[2,3,5–7,11,13] Determination of the metastatic location depends on imaging, especially MRI, when the extent of metastasis is too large to be confirmed by CT alone. In the case described here, CT scans showed a lesion located in the right ethmoid and sphenoid sinus upon the first transfer to the nasal cavity and paranasal sinus; after MRI, a tumor based on the ethmoid sinus was estimated and demonstrated by performing endoscopic surgery. Upon the second and third transfers, sinus

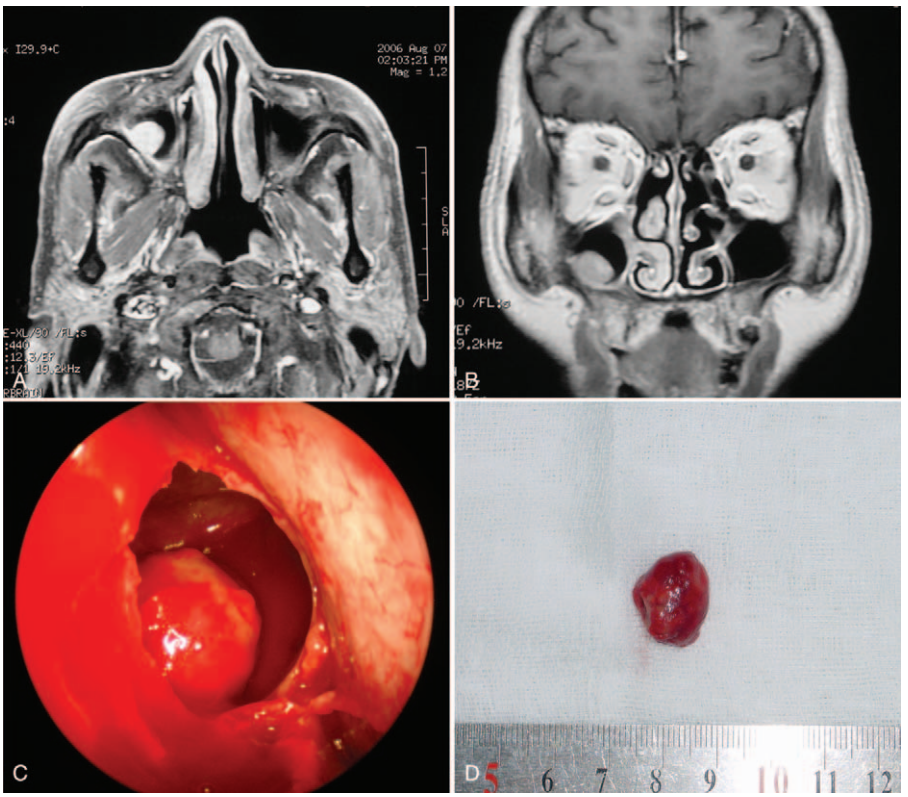

Figure 4. (A–D) ccRCC metastasis to the right maxillary sinus. (A) Axial MRI shows a strong, enhanced mass located at the right maxillary sinus, with a clear boundary. (B) Coronal MRI shows a well-defined mass with heterogeneous density at the right maxillary sinus. (C) Endoscopic surgery via the prelacrimal recess approach (PLRA) shows a smooth, easily movable mass with distinct edges located at the bottom of the maxillary sinus. (D) Pathological specimen examination shows smooth, reddish mass with a clear boundary, approximately 1.5 cm × 1.5 cm. MRI = magnetic resonance imaging, PLRA = prelacrimal recess approach.

metastases were confirmed by endoscopic resection, combined with CT and MRI.

Although rare, metastases to the nasal cavity and paranasal sinus are clinical features of ccRCC and should be detected by urologists and rhinologists. The metastatic mechanism remains unclear. Two potential hematogenous routes are reported: direct transfer of tumor emboli to the head and neck via Batson's plexus (extensive anastomoses between the avalvular vertebral and epidural venous system), in which the sinonasal region may be the only site of metastasis; and tumor metastases bypass the inferior vena cava, pulmonary capillary filtration system, cardiovascular system and maxillary artery, and concurrent lung or brain metastasis may be present.[13] Some researchers postulate a lymphatic route in which a tumor embolus flows to the regional lymphatics, into the thoracic duct and reaches the head and neck region via retrograde flow through intercostal, mediastinal, or supraclavicular lymph vessels to the subglottis and above.[2] Therefore, ccRCC repeatedly metastasizes to the nasal cavity and paranasal sinuses via multiple routes.

Table 1

Clinical manifestations and involved sites of nasal cavity and paranasal sinus metastases of ccRCC (28 cases).

	Frequency	Percentage %
Clinical manifestation		
Epistaxis	16	57.1
Nasal obstruction	10	35.7
Others	12	42.9
Involved site		
Nasal cavity	8	34.8
Ethmoid sinus	8	34.8
Maxillary sinus	8	34.8
Frontal sinus	2	8.7
Nasopharynx	2	8.7
Sphenoid sinus	1	4.3
Orbit	1	4.3

ccRCC = clear-cell renal cell carcinoma.

Only 10% of ccRCC patients present the classical triad of hematuria, costovertebral pain, and abdominal mass;[13] some patients may have no primary tumor symptoms, while others initially manifest with nasal symptoms.[14] In our review of 28 patients, epistaxis (16 cases, 57.1%) is the most common symptom (Table 1). Metastasis may manifest as nasal obstruction (10 cases, 35.7%) after a considerable tumor size is reached. When the tumor is located in the maxillary or frontal sinus, patients may present swelling of the cheek or frontal region as the tumor grows.[7] Some may experience headache, facial numbness, epiphora, exophthalmos, diplopia, decreased vision, and ptosis,[2,5] or an individual may only express a nasal tip mass.[12]

Epistaxis, a typical clinical manifestation, is closely related to the pathophysiological characteristics of ccRCC. ccRCC is reportedly associated with loss of function of the von Hippel Lindau gene, which leads to the upregulation of hypoxia inducible factor (HIF) and increased function of vascular endothelial growth factor (VEGF). This sequence of reactions eventually increases angiogenesis and the vascularity of ccRCC and its metastases.[13] Histopathologically, metastatic ccRCC

shows clear cell borders, eosinophilic cytoplasm, round or oval nuclei, and tumor cells arranged in nests with capillaries in between (see Fig. 2A). Immunohistochemical stains show that tumor cells with vimentin, EMA, CD10, CA IX, and PAX8 positivity may have diagnostic significance. Additionally, CD10 is useful for diagnosis and differential diagnosis of ccRCC metastasis, combined with medical history and lesion location[15] (see Fig. 2B). Therefore, sinonasal metastasis of ccRCC should always be considered when a patient presents epistaxis from a mass located in the nasal cavity and paranasal sinus.

It is difficult to distinguish such masses from primary malignant tumors or other metastases via imaging. The time-intensity curve (TIC) of dynamic contrast-enhanced MRI (DCE-MRI) indicates benign and malignant masses. Pathological examination is a gold standard for diagnosis, and a ccRCC history is conducive for diagnosis. Once pathological results suggest ccRCC, the kidney should be examined, as well as other sites where metastasis may occur, such as the lungs, brain and bone.

Radiotherapy, immunotherapy, and chemotherapy are the main reported treatments for ccRCC metastasis[2,3,5,11,13] because the hypervascular tumor causes massive intraoperative hemorrhage and is rarely completely resected. Therefore, endoscopic biopsy is recommended. Some researchers propose that intravascular embolization should be performed for bleeding control prior to surgery.[2,16] Indeed, it is possible to completely remove tumors with adequate hemostasis preparation preoperation and rapid removal of the tumor, combined with coagulation technology. Endoscopic surgery should be the first-line treatment, utilizing a transnasal approach to reach different anatomical sites. In the present case, a transnasal approach was employed after metastasis to the nasal cavity, and a PLRA was used to address the maxillary metastasis, which contributes to operation field keeping and hemostasis. An imaging guidance system (IGS) is helpful when the lesion extends to the orbit, pterygopalatine fossa, infratemporal fossa, sellar area, cavernous sinus, and low-level brain tissue. As tumors are usually covered with sphacelus, simple biopsy may lead to false negatives. Multiple biopsies may be required, and endoscopic surgery increases the positive rate and reaches the negative margins.

According to the 2017 National Association Cancer Network (NCCN) clinical trial guide (second edition), nephrectomy and resection of metastasis should be performed if the primary lesion is resectable and metastases are isolated, including those that metastasize initially or after a disease-free interval after nephrectomy. The guidelines indicate that this principle of surgery applies to pulmonary, osseous, and brain metastases. Primary and metastatic lesions may be removed simultaneously and treated with fractional resection,[17] as well as sinonasal metastasis.

Radiotherapy, target cell immunotherapy and chemotherapy are choices for those whose systemic condition is unable to tolerate general anesthesia or who have unresectable lesions.[7] Generally, ccRCC is a radio-resistant tumor due to the presence of normal tissue around the tumor, but studies show that metastases respond well to higher doses of radiation, and the local control rate is acceptable.[3] Other studies indicate that target cell immunotherapy is expected to cure ccRCC metastasis. Chemotherapy is usually administered for immunotherapy failures.[5]

The prognosis is generally poor when metastasis occurs, regardless of the interval between metastasis and primary nephrectomy; the 2-year and 5-year survival rates are 41% and 13%, respectively.[18] One study reported a survival time of 10.2 to 22 months.[16] Although most metastases recur at the same site after surgery, other studies suggest that surgery extends progression-free survival (PFS).[17] In the presented case, metastases to the right ethmoid sinus, left olfactory cleft, and right maxillary sinus were identified 6, 14, and 15 years, respectively, after the primary nephrectomy. Although multiple metastases occurred after endoscopic surgery, the patient survived for years and was followed for 20 years. The efficacy and prognosis of endoscopic surgery for the treatment of ccRCC metastasis to the nasal cavity and paranasal sinus require further study, as similar reports are rare.[14] The present case illustrates that endoscopic surgery plays a positive role in controlling symptoms, improving quality of life, and prolonging survival time; it recommends routine monitoring of the nasal cavity and paranasal sinus to ensure early detection, early diagnosis and early treatment.

4. Conclusion

Distant metastasis of ccRCC to the nasal cavity and paranasal sinus is rare, with varied biological characteristics in terms of growth rate, metastatic time, and spread pattern. Epistaxis may be the initial symptom of sinonasal metastasis. The most common sites for sinonasal metastases from ccRCC are the nasal cavity, ethmoid sinus, and maxillary sinus. Endoscopic surgery is recommended as a first-line treatment. Nasal cavity and paranasal sinus metastasis is a clinical feature of ccRCC. Thus, routine monitoring of the nasal cavity and paranasal sinus is essential over a lifetime and should be part of routine nasal examination. Metastasis to the nasal cavity and paranasal sinus should be considered when epistaxis arises.

5. Ethics

This case report was carried out with the approval of the Institutional Review Board (IRB) of Beijing Tongren Hospital (TRECKY2017-033), and with the informed consent of patients from the patient's guardian, because the patient died in 2011.

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Supervision: Qian Huang, Xiaohong Chen, Shunjiu Cui, Zhenxiao Huang, Yan Sun.

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