Renal Cell Carcinoma Metastases in the Head and Neck

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Renal cell carcinoma (RCC) is the most common malignant neoplasm of the kidney, and metastasis in head and neck areas are rarely described. We describe four cases of metastatic RCC in the head and neck areas treated between January 1995 and December 2004. The metastatic sites included the basal region of the tongue, parenchyma of the bilateral parotid glands, bilateral thyroid glands with left cervical lymphadenopathy, and frontal scalp. Three of the patients had previous primary RCC and underwent nephrectomy. Excluding the one patient in whom no primary tumor was found, the interval between the primary diagnosis and the metastatic disease ranged from two to eight years. Treatment included resection of the metastatic lesions for three patients, and palliative chemotherapy and radiotherapy for one patient. Of the three patients who underwent tumor resection, two achieved disease-free status and one died because of sepsis and multiple organic failure. In our experience and the experience of others, resection of solitary, organ-confined RCC metastases provides symptom relief and improves quality of life. *(Chang Gung Med J 2006;29(4 Suppl):59-65)*

Key words: renal cell carcinoma, metastasis, head and neck, tumor resection.

Renal cell carcinoma (RCC) represents 2% of all malignant cancers and occurs in a male-female ratio of nearly two to one. As there are no early warning signs, many patients are unaware they have metastases and only 25-30% have overt metastases at initial presentation.[1] The most frequent sites of multiple metastatic diseases are lung parenchyma (50-60%), bone (30-40%), liver (30-40%) and brain (5%).[2] The head and neck are unusual sites for metastases but skin, skeletal muscle, thyroid gland, nasal cavity and paranasal sinus metastases have been reported.[3-10] The common presenting symptoms of metastatic RCC in the head and neck are enlarged solitary mass, epistaxis, facial tenderness and nasal obstruction, depending on the tumor location and extent of invasion. Previous studies and reviews of RCC metastatic to the head and neck are rare. Richard Miyamoto[3] reported six cases and Pritchyk et al.[11] reported four. We present four cases of RCC metastatic to the head and neck. A literature review of treatment, mortality and prognosis is also presented.

Patients with malignant RCC diagnosed between January 1995 and December 2004 were identified from our hospital pathology database. A review of their pathology reports revealed four patients with a clinically recognized, solitary metastatic lesion in the head or neck. The presence of primary RCC was proved by biopsy or nephrectomy, and the primary RCC was treated with radical nephrectomy. Metastatic tumors were evaluated by clinical examination, laboratory examination and radiographic image studies. Diagnosis was proven by histological examination of biopsies (sonographic-

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guided needle biopsy or open biopsy) of the metastatic lesions. The pathological findings were reviewed by two pathologists, and local resection of the metastatic lesions in the head and neck was performed.

CASE REPORTS (see Table 1)

Case 1

A 76-year-old woman was referred to our Otolaryngology Department in October 2003 for evaluation of a large fungating mass (3 cm x 4 cm) at the tongue base, which was rapidly enlarging and had been bleeding intermittently for six months. In 1995, she had been diagnosed with a right RCC, which had been treated with right nephrectomy. In 2003, liver and right lung tumors were seen on chest X-ray and liver sonographic examination. Clinical symptoms of these tumors (massive hematemesis and dysphagia) were also noted. Physical examination revealed a fungating, bluish-purple lesion at the tongue base without cervical lymphadenopathy. T1W1 magnetic resonance image (MRI) showed a hyperintensive heterogeneous enhanced tumor located at the right lateral and posterior portion of the tongue. (Fig. 1) Biopsy demonstrated that these were RCC metastases. A wide resection hemiglossectomy with forearm free flap reconstruction was performed. The pathology report showed well-defined tumors with clean margins and intervening delicate vasculature. The patient died of pneumonia, sepsis and multiple organ failure one month after the operation.

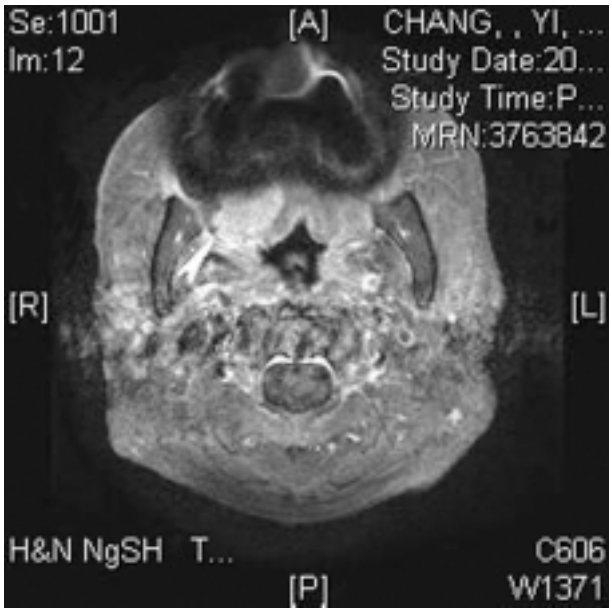

Fig. 1 MRI exam showed a hyperinetnsive heterogeneous enhancement tumor at lateral and posterior portion of right tongue on T1W1 image.

Case 2

A 56-year-old woman was known to have a right RCC, which had been treated with right nephrectomy three years ago. Spinal thoracic T4 vertebral body, left femoral bone and mediastinal tumor metastases were revealed on MRI examination and bone scan study six months after nephrectomy. The patient underwent radiotherapy (3300 cGy in 20 frac-

Table 1. Case Reports

Case	Age	Gender	Primary tumor		Metastases in head and neck				Other metastases	Survival
			Location	Treatment	Presenting symptoms	Location	Interval*	Treatment		
1	76	Female	Right kidney	Right nephrectomy	Hematemesis, dysphagia	Tongue base	8 years	Hemiglossectomy + flap reconstruction	Liver, lung	Died after 1 month
2	56	Female	Right kidney	Right nephrectomy	Bilateral cheek masses	Bilateral parotid glands	3 years	Bilateral parotidectomy	Femoral bone, T4 vertebral body, mediastinal mass	Disease free for 8 months
3	62	Male	Right kidney	Right nephrectomy	Right lower neck swelling masses, sudden-onset headache, vertigo	Thyroid gland, left cervical lymph node (zone III)	2 years	Radiotherapy (3750 cGy), interferon-α, interleukin-2	Brain (right parietal lobe)	Stable disease for 6 months
4	61	Male	Unknown	Follow-up	Body weight loss, right enlarging frontal mass	Right frontal scalp	0	Resection	Pelvic bone, T1 vertebral body	Alive for 6 months

Interval*: duration between nephrectomy and metastatic disease.

tions), chemotherapy (5-fluorouracil) and interferon-α (IFN-α) therapy for three months. She was referred to our otolaryngology service with a one month history of progressively enlarging masses in the bilateral cheek areas in July 2001. Clinical symptoms and physical examination revealed two solitary masses (3 cm x 3 cm and 3 cm x 4 cm) in the bilateral parotid glands without facial paralysis or local inflammation. Computerized tomographic (CT) examination showed heterogeneous hyperintensive tumors located in the anterior superficial part of the bilateral parotid glands. (Fig. 2) Core-needle aspiration biopsy under sonographic-guidance was performed and histology reports showed clear cell carcinoma. Bilateral superficial parotidectomy was performed. The pathological findings were consistent with metastatic RCC. The patient had no evidence of recurrent disease eight months after surgery.

Case 3

A 62-year-old man presented in May 2003 with a three week history of right lower neck swelling and sudden-onset headache, vertigo, nausea and vomiting. Medical history was significant for right RCC, which was diagnosed and treated with a right radical nephrectomy in 2001. Physical examination revealed a right-side tumor (6 cm x 3 cm) and left-side tumor (6 cm x 4 cm) on the thyroid gland, and a 2 cm x 1 cm tumor in the left cervical zone III area. No other active neurological symptoms or signs were found except left-side weakness, apparently the result of an old infarction. Histological evaluation of sonogram-guided needle biopsies of the two masses revealed metastatic RCC. (Fig. 3) Brain metastasis was diagnosed on the basis of a brain MRI examination and stereotaxic biopsy of the right parietal lobe lesion. The patient refused surgery but accepted a palliative course of radiotherapy and chemotherapy to control the metastatic lesions in the thyroid and brain. He received radiotherapy (3750 cGy in 35 fractions), and IFN-α and interleukin-2 (IL-2) therapy for three months. The metastatic lesions appeared with a stable 5-cm diameter tumor located on the right side of the thyroid gland at his six month follow-up visit.

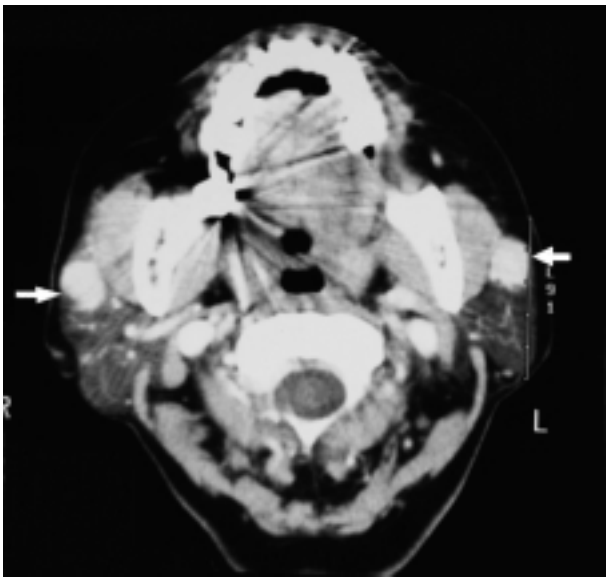

Fig. 2 CT exam showed heterogeneous enhancement, and hyperintensitive tumors located in the anterior superficial portion of the bilateral parotid glands.

Case 4

A 61-year-old man presented in February 1993 with weight loss (3 kg in four months), a one month history of a rapidly enlarging frontal mass and a history of diabetes. Physical examination revealed a 3 cm x 3 cm bony, slightly tender frontal mass without other tumor lesions found in the head and neck region. No significant neurological symptoms or signs were noted at presentation. Skull X-ray demonstrated an osteolytic lesion in the frontal region. A brain CT examination showed a tumor in the frontal scalp area with an extremely high concentration of

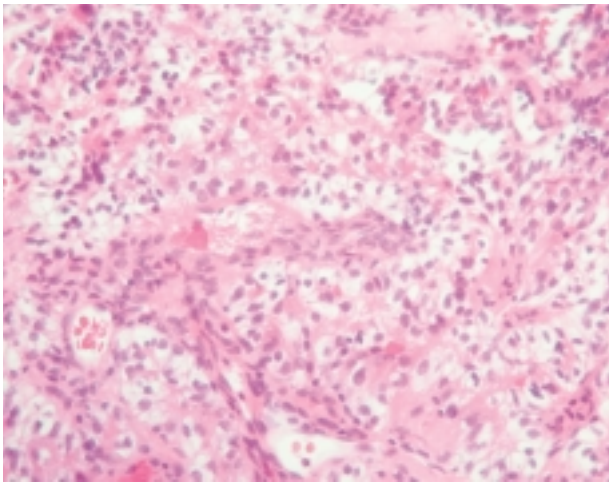

Fig. 3 Tumor cells had pleomorphic and hyperchromic nucleai and clear or eosinophilic cytoplasm. (H & E stain x400)

radioactivity. Frontal tumor excision was performed in February 1993. Pathology reports showed metastatic clear cell adenocarcinoma. Postoperative abdominal CT and sonographic examinations of the liver and bilateral kidneys showed no evidence of liver, spleen, intestine or kidney metastases. Under the diagnosis of unknown primary metastatic adenocarcinoma, the patient underwent radiotherapy (5000 cGy in 20 fractions) and chemotherapy (5-fluorouracil). Two years later, he presented with a two week history of tenderness in the back and pelvis. CT examination showed a left pelvic bone mass and left L1 vertebral body mass with bony destruction. Evaluation of a CT-guided core needle biopsy showed a malignant clear cell tumor. A second course of chemotherapy was given preoperatively. Laminectomy of the L1 vertebral tumor was performed in April 1996. The pathology reports were consistent with metastatic RCC. Previous pathological findings also demonstrated metastatic RCC in the frontal scalp region. Abdominal CT and sonographic examinations of the liver and bilateral kidneys still showed absence of liver, spleen, intestine and bilateral kidney involvement. Palliative radiotherapy was suggested but his family asked for an out-of-hospital referral at the six month follow-up visit.

DISCUSSION

RCC is the third most common infraclavicular tumor (after lung and breast carcinomas) that metastasizes to the head and neck. It occurs more frequently in the fifth or sixth decade of life and has higher incidence in males.[1] Metastases may spread to multiple regions of the body; the most common sites are lung parenchyma (50-60%), bone (30-40%), liver (30-40%) and brain (5%).[2] RCC metastases in the head and neck (the most common sites being the thyroid gland, nose and paranasal sinus, skin and larynx) were reported in 14-16% of patients. However, metastases solely in the head and neck occur only in 1% of patients with primary RCC.[6]

The pathogenesis of metastatic RCC has been postulated by Boles and Cerny,[6] and by Nahum and Bailey.[4] Possible metastatic routes to the head and neck include the (1) systemic circulation, (2) venous circulation, and (3) lymphatic circulation. The rich venous anastomosis with the prevertebral, vertebral and epidural system supports a pathway for the tumor to spread. Veins, which are valveless, offer an easy way for tumor emboli to spread with less resistance. Increase of intraabdominal or intrathoracic pressure causes a retrograde flow from the venous channels back through the prevertebral and vertebral venous plexus. In this way, renal carcinoma apparently can travel from the kidney, bypass the pulmonary capillary filtration, and metastasize in the head and neck. If there is no evidence of lung or liver disease, it has been postulated that tumor cells can migrate through Batson's venous plexus or the lymphatics via the thoracic duct. Thyroid glands are common sites for metastatic RCC in the head and neck, accounting for 50% of lesions.[7] Moreover, the nose and paranasal sinuses are also common metastatic sites.[3] Among our four cases, two were rare: one case (Case 2) of RCC metastatic to the bilateral parotid gland (not previously reported) and one case (Case 1) of RCC metastatic to the tongue. The most common site of lingual metastasis is the tongue basal region, which is believed to be due either to the rich vascular supply (*via* the dorsal lingual arteries) or to the relative immobility of this area.[8] RCC metastatic to the lymph nodes was seen in 58% of patients, frequently involving the pulmonary, tracheal and retroperitoneal lymph nodes.[9] Case 3 (RCC metastatic to the bilateral thyroid gland and cervical jugular lymph nodes) is also a rare case.

Nephrectomy may be justified in selected patients with metastatic disease when the intention is to improve the quality of life or local symptoms. However, it is not justified when the intention is to induce spontaneous tumor regression, which occurs in less than 1% of cases.[1] Also, the causal link between the removal of primary RCC and the spontaneous regression of metastases is uncertain. Comparing patients without nephrectomy to those with recurrence after nephrectomy, frequency of metastases to various organs (except brain and contralateral kidney) was similar.[9,16] In case 4, nephrectomy was not performed because no primary renal tumor was found and bilateral nephrectomy is associated with high morbidity, though metastatic RCC to the L1 vertebral body and pelvic bone was diagnosed. With solitary metastatic lesions in the head and neck, local resection of the metastases not only provides diagnostic evidence but also debulks the tumor. Gottlieb and Roland reported that excision of solitary metastatic disease after nephrectomy resulted

in a 2-year survival in 41% and 5-year survival in 13% of cases.[10] Pritchyk et al. also presented four cases of RCC metastatic to the head and neck, in which no residual or recurrent disease was found after the metastatic tumor was resected.[11] In our present cases, patients whose metastatic lesions were resected did not have residual or recurrent head and neck lesions.

RCC has been regarded as a radioresistant tumor. However, radiotherapy has been shown to be useful in the palliation of the tumor. Cases of bone, brain and soft tissue metastases have good response rates to high dose radiation. The significantly higher rate of good responses obtained with 4500 cGy in four and a half weeks indicates that carefully tailored doses can lead to better palliative results.[12]

Hormonal and chemotherapeutic agents have improved effect on RCC. The fluoropyrimidines such as floxuridine (response rate 14.6%) and 5-fluorouracil (response rate 10%) have the highest single agent activities.[13] IFN-α has a direct antiproliferative effect and IL-2 affects tumor growth by activating lymphoid cells *in vivo*.[1] Taro Shibayama reported complete disappearance of metastatic RCC in the tongue base after IFN therapy in one patient.[14] Approximately 10-20% of patients with metastatic RCC will have an objective response to IFN-α therapy. Floxuridine combined with IFN-α-2b or IL-2 achieved an overall response rate of 23% in cases of lung, soft tissue, bone, lymph node and liver metastases.[18] However, IFN and IL-2 by themselves should not be considered effective treatments for RCC because of poor response and no clear evidence of improved survival.[1]

The prognosis of patients with metastatic RCC is poor.[17] The major prognostic factors may be the disease-free interval and anatomic extent of the tumor. In a study by O'dea et al., 44 patients with RCC and a solitary metastatic lesion were separated into two groups: Group 1 patients (those presenting with RCC and concomitant metastases) were mostly dead within two years (2-year survival rate was 22%); Group 2 patients (those presenting with metastases after nephrectomy) had a better prognosis (5-year survival rate from the time of nephrectomy was 50%). The median time before a relapse after nephrectomy was 15-18 months and 85% of the relapses occurred within three years.[15] In general, the longer the disease-free interval from diagnosis to presentation of metastatic disease, the longer the survival. The metastasis also affects survival. Patients with solitary, organ-confined tumors (i.e. completely resectable tumors) have better outcomes than those with nodal involvement or multiple distant metastases. The other prognostic factors (such as histological pattern, nuclear grade and DNA content) are less well established and influential.[1,9]

Although metastatic RCCs of the head and neck are rare, the otolaryngologist must keep these in mind when evaluating metastatic lesions, especially in those patients with a medical history of previous RCC. Our study is limited by its retrospective nature and the small number of patients. Nonetheless, it presents the variations in the pattern of metastatic spread to the head and neck, and demonstrates that metastatic tumor resection can be beneficial when the intent is to provide symptom relief and improved quality of life. Tailored radiotherapy should be attempted in all cases. Chemotherapeutic agents have little effect on RCC but they may be used as adjuvant therapy for recurrent disease. Further research is needed to develop effective therapeutic agents for the treatment of RCC and its metastases.

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腎細胞癌轉移至頭頸部

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腎細胞癌 (RCC) 是最常見之腎惡性腫瘤。轉移至頭頸部的腎細胞癌並不常見。針對這些轉移病灶的治療仍是臨床醫師的一項挑戰。統計自 1995 到 2003 年本院共計四例病例爲腎細胞癌轉移至頭頸部；轉移部位分別爲：舌根部 (一例)，兩側腮腺 (一例)，兩側甲狀腺合併左側淋巴結 (一例) 與額部皮膚 (一例)。病患有原發腎細胞癌接受腎切除手術，其轉移病灶發現時間間隔爲 2 至 8 年。其中三例病患接受手術切除頭頸部轉移病灶，其中一例病患於術後一個月因肺炎引發敗血症及多重器官衰竭死亡。一例病患接受化學治療合併放射治療後六個月仍有甲狀腺病灶持續追蹤。結論：針對轉移至頭頸部的腎細胞癌，切除轉移病灶的治療目的主要在於改善病患症狀與生活品質。化學治療合併放射治療回溯文獻報告對於此轉移病灶之治療仍無良好之預後。因病例尚屬少見，特此提出報告。(長庚醫誌 2006;29(4 Suppl):59-65)

關鍵字：腎細胞癌，遠端轉移，頭頸部，腫瘤切除。

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