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Clinicopathological features of our renal cell carcinoma metastasis cases: A single-center experience

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Abstract

Renal cell carcinoma (RCC) is the most common renal tumor in adults, arising from renal tubular epithelial cells. Approximately 30% of patients with RCC have metastases at the time of diagnosis, while metastases can be seen in 40% of patients during follow-up after nephrectomy. Metastases most commonly occur in the lung, bone, and lymph nodes. In our study, we aimed to retrospectively examine the cases diagnosed with RCC metastasis and evaluate their clinicopathological features. Age, gender, metastasis site, number of metastatic foci, localization of primary kidney tumor, histopathological type of primary kidney tumor, diameter of primary kidney tumor, grade of primary kidney tumor, and survival status of 52 patients diagnosed with RCC metastasis were recorded. Eleven (21.2%) of the cases had primary RCC and simultaneous (synchronous) RCC metastasis in the kidney. In 27 (51.9%) cases, RCC metastasis was detected in the follow-up period (metachronous) after nephrectomy due to the diagnosis of primary. The number of patients who were initially diagnosed with RCC metastasis and then were found to have primary RCC in the kidney was 14 (26.9%). Thirty-nine (75%) cases had a single metastatic focus. Metastasis site distribution of the cases; bone 18 (34.6%), lung 16 (30.8%), lymph nodes 8 (15.4%), liver 6 (11.5%), adrenal gland 6 (11.5%), brain 4 (7.7%) was. RCC metastases can occur as metastatic disease before primary tumor diagnosis, at the time of primary tumor diagnosis, or years after nephrectomy.

Keywords: Renal cell carcinoma, metastasis, neoplasm

Introduction

Renal cell carcinoma (RCC) is the most common renal tumor in adults, arising from renal tubular epithelial cells. RCC is responsible for approximately 2% of all cancer diagnoses and cancer-related deaths [1]. The incidence increases with age. It peaks in the 6th and 7th decades. It is more common in men than in women [2]. There are three main subtypes of RCC: clear cell, papillary, and chromophobe. Clear cell RCC (75%) is the most common subtype. This is followed by papillary (15%) and chromophobe (5%) subtypes [3].

RCC may not be clinically symptomatic for a long time. Flank pain, hematuria, and a palpable mass are the classic clinical signs. Hematuria is the most valuable diagnostic clinical sign. However, classical symptoms are not observed in most of the patients and the tumor is detected incidentally in approximately 60% of the patients. The development and widespread use of imaging methods increase the incidental diagnosis of kidney tumors [1]. While metastasis is detected at the time of diagnosis in approximately 30% of patients with RCC, metastasis can be seen in 40% of patients during follow-up after nephrectomy [1,4,5]. Eighty five percent of RCC metastases occur within the first three years [6]. RCC metastasizes both by hematogenous and lymphatic routes. Due to the high vascularity of the tumor, it has the potential to metastasize to different tissues and organs. Metastases most commonly occur in the lung, bone, and lymph

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nodes. However, it can metastasize to many different regions such as the liver, adrenal glands, contralateral kidney, brain, thyroid, testis, and skin [4,7]. The main treatment in RCC is surgery. It is a tumor resistant to chemotherapy and radiotherapy. Targeted therapies are applied in metastatic RCC cases [1]. Five-year survival in RCC cases is over 80%. In metastatic cases, the 5-year survival rate falls below 10%. The presence of metastases at the time of diagnosis is considered the most important negative prognostic parameter [8].

In our study, we aimed to examine the clinicopathological features of the cases diagnosed with RCC metastasis between January 2006 and December 2022 and to evaluate them in light of the literature.

Material and Methods

Our study was planned retrospectively. The study was carried out with the approval of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (Date: 08.06.2023 Decision No: 23-KAEK-135).

In our study, 52 cases who were diagnosed with RCC metastasis by histopathological examination in the Department of Medical Pathology between January 2006 and December 2022 were included. The pathology reports of the cases were reviewed retrospectively by scanning from the pathology archive. Hematoxylin-eosin-stained preparations of the cases were reviewed again. Age, gender, location of metastasis, number of metastatic foci, localization of primary kidney tumor, histopathological type of primary kidney tumor, diameter of primary kidney tumor, grade of primary kidney tumor, and survival status were recorded from pathology reports and records in the automation system. Histopathological typing of the primary tumor was performed according to the World Health Organization (WHO) 2016 classification of kidney tumors. The Fuhrman grade system, which is the most widely used system, was used for the grade of the primary tumor. The Fuhrman grade system is a four-stage grading system. Grading was done by evaluating the nuclear size, nuclear shape features, chromatin pattern, and nucleolar prominence in tumor cells.

Statistically, categorical measurements were specified as numbers and percentages, and continuous measurements were expressed as mean and standard deviation (median and minimum-maximum where necessary). SPSS 22 package software was used for the analysis.

Results

A retrospective review of our archive of the Medical Pathology laboratory between January 2006 and December 2022 revealed 52 cases with a diagnosis of RCC metastasis. The ages of 52 patients diagnosed with RCC metastases were between 38 and 81 years, with a mean age of 63.8 years. Thirty-five (67.3%) of the cases were male and 17 (32.7%) were female. The mean age of the female cases was 67.6 (56-81) and the mean age of the male cases was 62 (38-79).

Eleven (21.2%) of the cases had primary RCC and simultaneous (synchronous) RCC metastasis in the kidney. In 27 (51.9%) cases, RCC metastasis was detected in the follow-up period (metachronous) after nephrectomy due to the diagnosis of primary RCC. The mean duration of metastasis in these cases was 26.1 months (1-84 months). The number of patients who were initially diagnosed with RCC metastasis and then were found to have primary RCC in the kidney was 14 (26.9%). There was a single metastatic focus in 39 (75%) cases. The number of cases with two or more metastatic foci was 13 (25%). The metastasis site distribution of the cases (Figure 1) was as follows: bone 18 (34.6%) (Figure 2a), lung 16 (30.8%) (Figure 2b), lymph node 8 (15.4%), liver 6 (11.5%) (Figure 2c), adrenal gland 6 (11,5%) (Figure 2d), brain 4 (7.7%) (Figure 3a), pancreas 2 (3.8%) (Figure 3b), testis 1 (1.9%) (Figure 3c), thyroid 1 (1.9%) (Figure 3d), contralateral kidney 1 (1.9%), the other 3 (5.8%).

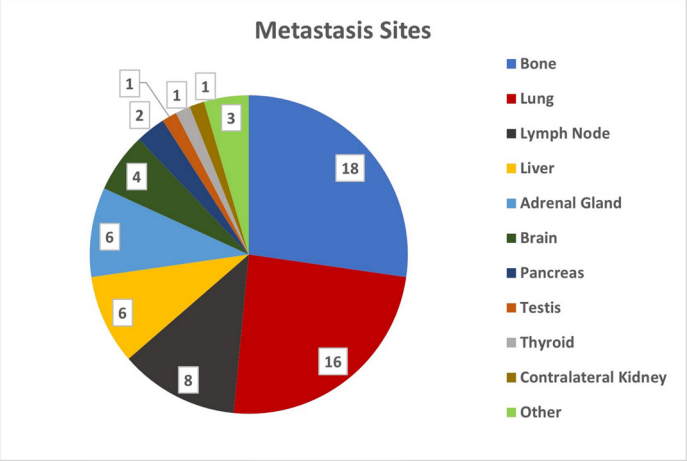

Figure 1. The metastasis site distribution of cases

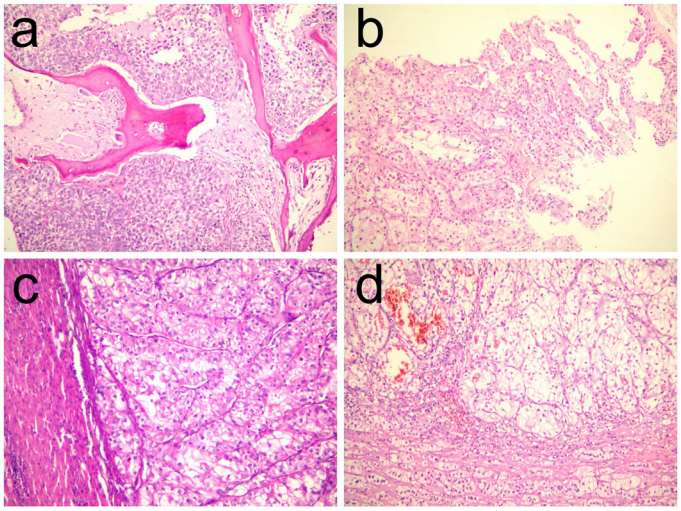

Figure 2. a. RCC infiltration in bone tissue (HEx100) **b.** RCC infiltration adjacent to alveolar structures in lung tissue (HEx100) **c.** RCC infiltration in liver tissue (HEx100) **d.** RCC infiltration in the adrenal gland (HEx100)

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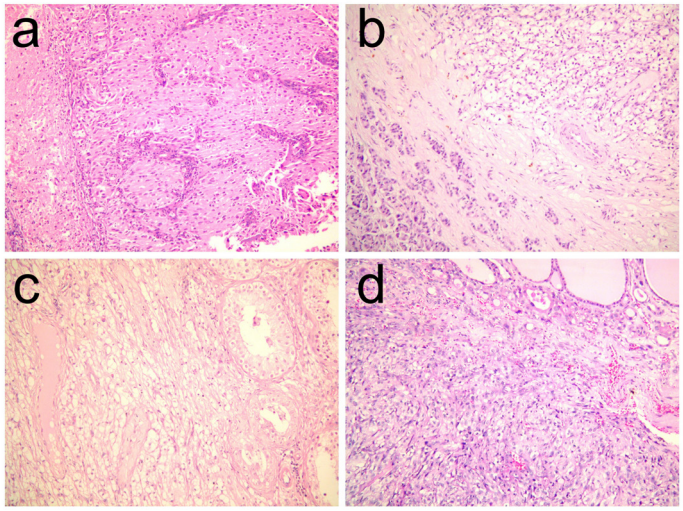

Figure 3. a. Glial cells and RCC infiltration in brain tissue (HEx100) **b.** RCC infiltration in pancreatic tissue (HEx100) **c.** Seminiferous tubules and RCC infiltration in testis tissue (HEx100) **d.** RCC infiltration in thyroid tissue (HEx100)

The localization of the primary tumor in patients with RCC metastasis was left kidney in 29 patients (55.8%) and right kidney in 23 patients (44.2). Macroscopic tumor diameters ranged from 3.5 to 16 cm, with an average of 8.8 cm. According to the histopathological type, 44 (84.6%) patients had clear cell RCC, 5 (9.6%) papillary RCC, 2 (3.8%) chromophobe RCC, and 1 (1.9%) patients had unclassifiable RCC. Fuhrman nuclear grade values; 2 cases (3.8%) were Grade 1, 9 cases (17.4%) were Grade 2, 28 cases (53.8%) were Grade 3, and 13 cases (25%) were Grade 4. Renal capsule invasion was detected in 84.6% of the cases, and perirenal adipose tissue invasion was found in 69.2% of the cases. Tumor invasion/thrombus in hilar vascular structures was present in 23% of the cases, and lymphovascular invasion in 42.3% of the cases. The mean survival time was 24 months (0-120 months) in 16 patients with a diagnosis of RCC metastasis who remained under follow-up.

Discussion

RCC accounts for 90% of kidney cancer cases. RCC is an aggressive tumor with the potential to metastasize. It is the 3rd most common urogenital cancer after prostate and bladder cancers [4,9]. It is among the top 10 most common cancers in the world. Its incidence is increasing in developed countries [1,3]. It is known that acquired factors such as gender, smoking, obesity, hypertension, acquired cystic kidney disease, occupational chemical exposures, and genetic predisposition play a role in the pathophysiology of RCC [3]. Flank pain, hematuria, and palpable abdominal mass symptoms, as well as fever, hypercalcemia, and erythrocytosis due to paraneoplastic syndrome can be seen in RCC. One-third of the patients present with metastatic disease and related symptoms [1,10]. With the increase in the use of radiological imaging methods such as ultrasonography and abdominal tomography, the incidental diagnosis of kidney tumors and the incidence of RCC have increased [9]. Partial or radical nephrectomy is the treatment of choice for localized RCCs confined to the kidney. It is highly resistant to chemotherapy and radiotherapy. Although metastatic RCC is resistant to conventional chemotherapy, advances in treatment have been made in recent years with the use of targeted agents (inhibiting vascular endothelial growth factor (VEGF) and its receptor (VEGFR)) [1]. Radiotherapy can be used as a palliative treatment in patients with brain or bone metastases [11].

The incidence of RCC increases with increasing age. It is generally two times more common in men than in women. In the Surveillance, Epidemiology and End Results (SEER) data, the mean age of RCC cases was reported as 64 [12]. A study examining 11157 metastatic RCC cases reported that the average age was 64 and 64% of the cases were male [7]. Similarly, in our cases, the mean age was 63.8 years, and the rate of male patients (67.3%) was high.

RCCs have subtypes with different molecular, morphological, immunohistochemical features and prognoses. Clear cell, papillary, and chromophobe RCC are the 3 main histopathological subtypes. The most common and most malignant subtype is clear cell RCC. It accounts for approximately 75% of RCCs and originates from the proximal tubule epithelium. Microscopic examination reveals a vascular pattern of cells with clear or eosinophilic cytoplasm and thin-walled blood vessels in the tumor. Immunohistochemical analysis shows positive staining with PAX-2, PAX-8, renal cell carcinoma marker (RCCma), CD10, Carbonic anhydrase-IX (CA-IX), low molecular weight cytokeratin (LMWCK), epithelial membrane antigen (EMA), and vimentin. No expression is seen with cytokeratin 7 (CK7), cytokeratin 20 (CK20), CD117, E-cadherin, and AMACR. Papillary RCC accounts for approximately 15% of kidney cancers and is the second most common subtype. It originates from the proximal tubule epithelium. Microscopic examination reveals true papillary structures with fibrovascular cores and tumor cells lining the tubules, foamy macrophages, and psammoma bodies. Chromophobe RCC occurs in approximately 5%. It originates from the distal tubule epithelium. In microscopic examination, tumor cells that form solid layers separated by hyalinized vascular septa, often with binuclear perinuclear halo, are observed. Tumors with histomorphological features other than known subtypes are referred to as unclassifiable RCC [9,13]. In our study, the most common subtype was clear cell RCC with 84.6%. This was followed by papillary RCC (9.6%) and chromophobe RCC (3.8%).

The pathological tumor stage is considered the most important prognostic factor. TNM system, which is determined according to tumor diameter and tumor invasion status, is used for staging. In TNM classification, tumor size, invasion of the venous system, invasion of the tumor into the collecting system, adrenal gland, renal capsule, and Gerota's fascia (T), involvement of lymph nodes (N), and presence of distant metastases (M) are evaluated. In two separate studies, retrospectively examining RCC cases, tumor diameters were found to be 6 cm and 7.65 cm

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on average [9,11]. In our study, the mean diameter of tumors in the kidney was 8.8 cm. Since all of our cases were metastatic, it was stage 4. The Fuhrman grade system is the most widely used histopathological grading system in RCC. It is one of the important prognostic factors in RCC. In a study of RCC cases, the rates of patients with Fuhrman stages 1, 2, 3, and 4 were 5.2%, 61%, 23%, and 7.8%, respectively [9]. In our cases, the rates of patients with a Fuhrman grade of 1, 2, 3, and 4 were 3.8%, 17.4%, 53.8%, and 25%, respectively. Since our study included patients with metastatic RCC, patients with grade 3 and grade 4 comprised approximately 80% of all cases.

Metastasis is the spread of tumor cells through the blood vessel or lymphatic system to distant or near sites different from the tissue or organ from which they originated. Clear cell RCC usually metastasizes by a hematogenous route. It goes to the pulmonary system via the renal vein and vena cava. It proceeds to the paravertebral venous plexus and pelvic veins via the lumbar veins. In this way, it makes metastases to the central nervous system, head and neck region, and bone. It can metastasize to hilar, aortic, caval, and thoracic lymph nodes via the lymphatic system. Apart from the usual metastatic spread of RCCs, metastases to anatomically distant sites have also been reported. Experimental studies are showing that metastasis occurs at the beginning of the life cycle of tumor cells [4,14,15].

In metastatic RCC cases, the number of metastatic sites and the sites and organs of metastasis affect the prognosis [16]. In a study in which metastatic RCC cases were examined, the rate of patients with a single metastatic focus was 61%, and the rate of metastasis to two or more sites was reported as 39%. The general distribution of metastatic locations are respectively; lung (45.2%), bone (29.5%), lymph node (21.8%), liver (20.3%), adrenal gland (8.9%), brain (8.1%) [7]. In another study, they reported the distribution of metastasis in patients with RCC metastasis as bone (56.2%), lung (31.2%), and adrenal gland (6.3%) [11]. In our study, in which we examined RCC metastasis cases, the most common metastasis locations were bone, lung, lymph node, liver, and adrenal gland. Single metastatic focus was seen in 75% of cases, and two or more metastatic foci were seen in 25% of cases. Our findings were consistent with the literature.

Bone metastases are seen in approximately 30% of RCC metastases. Bone metastasis is the second most common site of metastasis in RCC. Bone metastases are most common in the spine, pelvis, and proximal femur. It has been reported that the prognosis of cases with long bone metastases is better than those with spinal and sacrum metastases [2,17]. Bone metastases are considered an independent poor prognostic factor. Renal tumor cells mostly secrete IL-6. These cytokines stimulate osteoclasts and prevent apoptosis of malignant tumor cells [18,19]. In our case series, bone metastases were detected in 18 (34.6%) patients. The most common site of metastasis in our series was bone. Five patients were diagnosed with bone metastases before the diagnosis of primary RCC. In our cases with bone metastases, 10 had long bone involvement, 5 had spine involvement, and 3 had pelvis involvement (Figure 2a).

RCC metastasis mostly to the lung with a rate of 50-60%. Because RCC is a highly vascular tumor, lung metastasis is common. It can metastasize to the endobronchial region, lung parenchyma, or pleura [20]. In our series, the second most common lung metastasis was seen with 16 (30.8%) cases (Figure 2b).

Metastases can be seen simultaneously with the primary tumor or years after the primary tumor diagnosis. The biology of this condition has not been fully elucidated. It is explained by the inability to detect the association of metastasis with the primary tumor or the tendency of the metastasis to grow very slowly. Adrenal metastases of RCC are usually asymptomatic. Adrenal metastases are seen in 3.4% on the ipsilateral side and in 0.39-1.1% on the contralateral side. In a study of patients with RCC, 23 of 617 cases had adrenal metastases. Of these cases, 16 were reported as ipsilateral, 1 as contralateral, and 6 as bilateral [21,22]. In our study, adrenal gland metastasis was seen in 6 (11.5%) cases. Of these cases, 4 were ipsilateral, 1 was contralateral, and the other was bilateral. (Figure 2d).

Another common site of metastasis of RCCs is the brain. The incidence of brain metastases has been reported as 2-17%. Central nervous system symptoms are seen in approximately 70% of cases. Due to the vascularity of the tumor, intracranial hemorrhages are frequently seen [23]. In our study, brain metastasis was detected in 4 (7.7%) cases (Figure 3a).

Metastatic masses in the pancreas constitute 2% of all pancreatic malignancies. Pancreatic metastasis of RCC is a very rare condition. Studies have reported that the average time between nephrectomy and the development of pancreatic metastasis is 8 years. Aggressive surgical interventions are recommended in the treatment approach of pancreatic metastases [24,25]. In our case series, pancreatic metastasis was observed in 2 (3.8%) patients. In one of our cases, pancreatic metastasis was detected 3 years after the nephrectomy, and Whipple operation was performed for therapeutic purposes (Figure 3b).

Metastatic disease of the testicles is rare. Its incidence has been reported to be approximately 0.3-3.6%. RCC rarely metastasizes to the testicles. The relatively low temperature of the scrotum and the presence of the blood-testicular barrier play a role in the prevention of testicular metastases. Testicular metastases are usually painless and diagnosed with a scrotal mass [26,27]. In one of our cases (1.9%), RCC metastasis was observed in the contralateral testis 1 year after nephrectomy (Figure 3c).

Metastases constitute 1.1-3% of all thyroid cancers. RCC is known as the most common tumor that metastasizes to the thyroid gland. After nephrectomy, metastasis in the thyroid gland occurs approximately 7.5 years. As the time between the diagnosis of a primary kidney tumor and the detection of thyroid metastasis increases, the survival time increases positively [4,28]. In our series, RCC metastasis involving bilateral thyroid lobes was observed in 1 (1.9%) patient (Figure 3d).

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RCC is a highly metastatic tumor with unpredictable spread potential. Apart from known metastatic sites, RCC metastases have also been reported in tissues and organs such as skin, orbit, parotid gland, nose, paranasal sinuses, oral cavity, tongue, tonsil, heart, carotid body, ovary, uterus, skeletal muscle [4,29].

The limitations of our study are the small number of cases, the data obtained retrospectively, the records of clinical findings limited to the information in the automation system, and possible data losses. Because clinical trials and large case series in oncologic pathology studies are not always possible, sharing available reports, observations, and experiences is valuable.

Conclusion

RCC is an aggressive tumor with a high potential to metastasize. RCC metastases may present with very different clinical presentations as metastatic disease before primary tumor diagnosis, during primary tumor diagnosis, or years after nephrectomy. In patients with a history of malignancy, metastasis should be considered in the differential diagnosis of abnormal development in all kinds of tissues and organs. Due to the unpredictable biological behavior of RCC, long-term regular follow-up of these patients is recommended.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was carried out with the approval of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (Date: 08.06.2023 Decision No: 23-KAEK-135).

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