



Rare locations of metastatic renal cell carcinoma: A presentation of three cases

Retka mesta metastatskog karcinoma bubrežnog parenhima

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Abstract

Introduction. Metastatic renal cell carcinoma (RCC) frequently spreads not only to neighboring lymph nodes, but also to distant organs, including the lungs, liver, bones and brain. **Case report.** We presented three cases of RCC with colon metastasis. In the first, 63-year-old patient, after left nephrectomy followed with lymphadenectomy in paraaortic lymph node, left hemicolectomy was done due to RCC metastasis in rectosigmoid colon. In the second, 35-year-old patient, left radical nephrectomy was followed two years later with partial right nephrectomy, lung metastasectomy, small bowel and cecum resection and right orchiectomy all as

separate procedures in different time intervals. The patient died from brain and bone metastases two years after the first surgery. The third, 35-year-old patient, had right nephrectomy followed by repeated lymphadenectomies after 6, 12 and 24 months. Four years later RCC spreaded to cecum and right hemicolectomy was performed. **Conclusion.** RCC treated with nephrectomy should be carefully followed up with imaging methods as a proper treatment of RCC metastases to distant organs could be important for a patient survival.

Key words:
carcinoma, renal cell; neoplasm metastasis; urologic surgical procedures; treatment outcome.

Apstrakt

Uvod. Tumori bubrežnog parenhima (*renal cell carcinoma* – RCC) čine 3% maligniteta odraslih osoba. Najčešća lokalizacija metastaza RCC je u plućima, limfnim žlezdama, jetri i kostima, ali se u retkim slučajevima nalaze i u drugim organima. **Prikaz bolesnika.** Dve godine nakon radikalne levostrane nefrektomije zbog RCC, 63-godišnjem bolesniku je učinjena limfadenektomija zbog metastaze RCC u paraaortalnu limfnu žlezu. Deset meseci kasnije, učinjena je levostrana hemikolektomija zbog metastaze RCC u rektosigmoidni kolon. Kod drugog bolesnika, starog 37 godina, dve godine nakon levostrane radikalne nefrektomije zbog RCC, urađena je parcijalna desnostrana nefrektomija. U daljem periodu praćenja bolesnika, urađeno je više hirurških zahvata u cilju uklanjanja metastaza iz različitih organa: metastazektomija pluća, resekcija tankih creva i cekuma, i desnostrana orhiektomija. Dve godine nakon primar-

nog hirurškog zahvata došlo je do letalnog ishoda usled širenja bolesti na koštani sistem i mozak. Treći bolesnik, star 35 godina, nakon desnostrane nefrektomije zbog metastatskih promena RCC u limfnim žlezdama prošao je kroz limfadenektomije 6, 12 i 24 meseca nakon primarne operacije. Kod istog bolesnika četiri godine nakon primarne operacije, učinjena je desnostrana hemikolektomija zbog metastatske promene RCC u cekumu. **Zaključak.** Praćenje bolesnika nakon nefrektomije zbog RCC uz korišćenje metoda snimanja u određenim vremenskim intervalima doprinosi pravovremenom otkrivanju metastaza. Primena odgovarajućeg hirurškog zahvata u ranoj fazi poboljšava produžavanje i popravља kvalitet života bolesnika.

Ključne reči:
karcinomi bubrežnog parenhima; neoplazme, metastaze; hirurgija, urološka, procedure; lečenje, ishod.

Introduction

Renal cell carcinoma (RCC) is the third most common urogenital malignancy and present 3% of all malignancies in adults¹. Although 50% of all RCC cases are diagnosed by imaging techniques in an early, asymptomatic phase, 20–30% of patients already have metastatic disease². Moreover, 20–40% patients with localized RCC will develop local RCC recurrence or distant metastasis³. RCC metastases are usually located in the lungs, lymph nodes, liver, bones and suprarenal gland, but they can rarely be found in other organs. We presented three cases with RCC metastasis in different locations.

Case 1

A 63-year-old man was admitted to the hospital after a mass of 72 × 36 mm was detected in his left renal region. Two years earlier, the patient had been submitted to left radical nephrectomy, and pathology had confirmed RCC. Multislice computed tomography (MSCT) had not revealed any changes in the thorax and abdomen. A mass localized behind the tail of the pancreas, near the aorta was removed through a subcostal incision (in the same line as the scar from the previous surgery). Pathology confirmed paraaortic lymph node RCC metastatic disease, but did not reveal any malignant cells in other lymph nodes. Ten months later, the patient returned with irregular stools and bloating, and an ultrasound study showed a hyperechogenic structure localized in the left paraumbilical region just under the skin. Although abdominal MSCT excluded local tumor recurrence or organ and abdominal wall changes, colonoscopy revealed a vegetative 2 cm tumor, localized in the sigmoid colon 30 cm from the anus, and the patient went through hemicolectomy. Intraoperative findings included infiltration of the sigmoid colon wall and serosa by tumor, and enlarged mesenteric lymph nodes (Figure 1), and pathology confirmed RCC metastasis to the colon. Comparative histological and immunohistochemical analysis showed identical type of RCC in the kidney, lymph nodes and colon.



Fig. 1 – A resected sigmoid colon with intraluminal renal cell carcinoma (RCC) metastasis.

Case 2

A 35-year-old man with the history of left radical nephrectomy for RCC followed by chemotherapy (interferon alfa for 12 months and vinblastine for 11 months) was admitted in our hospital because of solid mass near the lower pole of the right kidney discovered in the follow-up study. Diagnostic evaluation before nephrectomy included MSCT which had shown large (10 × 13 × 14 cm) left kidney tumor and bilateral lung nodular metastasis up to 35 mm in diameter (Figure 2). Pathology revealed RCC stage III, nodular gland (NG) 3 with fields of bleeding and necrosis, with light granular cells and tumor infiltrated renal capsula, lymph nodes and blood vessels (pT3a Nx Mx). Postoperatively, during chemotherapy, the follow-up study including MSCT of abdomen and thorax were performed. One year after the surgery, control MSCT showed just one nodular change without progression in the left posterobasal lung which was recorded two months after the surgery.



Fig. 2 – A large left kidney tumor.

Fifteen months after the surgery, MSCT revealed a 30 mm nodular metastasis in the left lower lung (Figure 3) and a 3 cm solid mass near the lower pole of the right kidney, below the hilus (Figure 4). Because of these findings, MSCT performed before nephrectomy was reviewed again, and reassessment showed that this solid mass was present in the initial study, but it was smaller and was diagnosed as a cyst (Figure 5). In response to these findings, the patient underwent right partial nephrectomy, and pathology revealed clear cell RCC Fuhrman grade II (pT1a, L0V0). One month later, the patient underwent left lung metastasectomy which included removal of four different lesions of different dimensions (60 mm, 45 mm, 30 mm and 25 mm). Pathology examination of these lesions confirmed that they were metastatic of RCC origin.

However, two and half months after the last operation, the patient came to the Emergency Department for nausea



Fig. 3 – Nodular renal cell carcinoma (RCC) metastases in the lung.

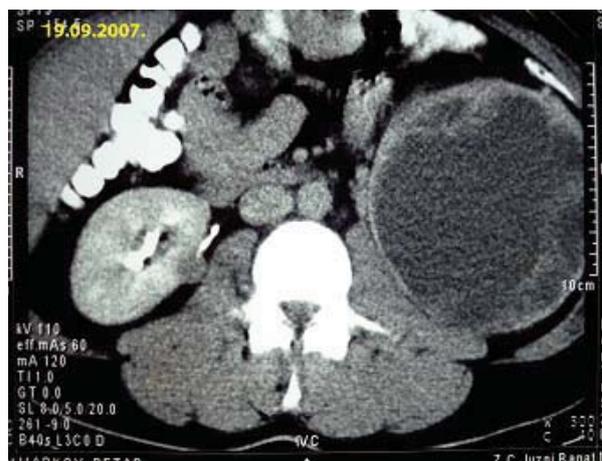


Fig. 5 – Initial MSCT before any surgery shows a large left kidney tumor and a small cystic formation on the right kidney considered at this moment as a simplex cyst.



Fig. 4 – A 3 cm renal cell carcinoma (RCC) at the solitary right kidney, previously considered as a small simplex cyst (see Fig. 5).

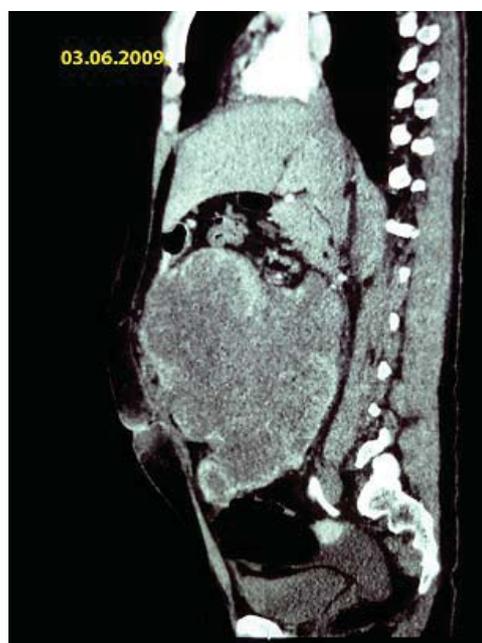


Fig. 6 – MSCT shows a big intaperitoneal lobular mass originating from the abdominal wall, involving the rectus abdominis muscle.



Fig. 7 – Tumor mass extirpation, small bowel and cecum resection and termino-lateral ileocolonic anastomosis [pathology examination showed a high grade renal cell carcinoma (RCC) metastasis in the large bowel and fat tissue].

and vomiting. His abdomen was distended and tender to palpation, and laboratory studies showed anemia (hemoglobin 88 g/L^{-1} , hematocrit 28%). Abdominal ultrasound examination showed a cystic formation, and MSCT revealed a solid hyperdense mass ($38 \times 35 \text{ mm}$) in the left lung and a big intaperitoneal lobular mass originating from the abdominal wall and involving the rectus abdominis muscle (Figure 6). The patient underwent surgery that included tumor mass extirpation, small bowel and cecum resection and termino-lateral ileocolonic anastomosis (Figure 7). Pathology examination showed a high grade RCC metastasis in the large bowel and fat tissue. Postoperatively, the patient also complained of painful right testis, and physical examination revealed a palpable 15 mm mass in the scrotum.

Although biochemical markers, alpha-fetoprotein (AFP) and beta human chorionic gonadotropin ([Beta HCG]) were normal, ultrasound examination showed a 21 mm echoheterogeneous mass that was clearly differentiated from other tissue in the right testis (Figure 8). The patient then had right orchectomy, and pathology confirmed that this testicular mass was metastatic RCC. Then, one month later, bone scintigraphy detected a left parieto-temporal bone metastasis (Figure 9), and head MSCT detected multiple brain metastases. At this point the patient received three cycles of chemotherapy with temsirolimus. From this point on, the patient's condition continued to deteriorate, and the patient died two and a half years after his primary operation.



Fig. 8 – Ultrasound examination showed a 21 mm echoheterogeneous mass [renal cell carcinoma (RCC) metastasis] in the right testis.

metastasis in three stages 6, 12 and 24 months after the primary surgery, was admitted in our hospital for primary disease evaluation. His main symptoms were pain in the right thigh and frequent liquid stools alternating with constipation. Although biochemical parameters and abdominal CT were normal, colonoscopy revealed submucosal tumorous 3 × 3 cm lesion across the ileocecal valve, and the patient underwent right hemicolectomy. Pathology revealed a large (5 cm) colon metastasis of RCC, but analysis of 13 lymph nodes showed reactive inflammation without evidence of malignancy. Chemotherapy consisted of interferon alpha (IFN-alpha) and 5-fluorouracil for three months. Follow-up evaluation (including imaging) nine months later did not reveal any RCC recurrence, and the patient was sent back to his referring hospital for the regular follow-up care.

Discussion

Despite modern diagnostic techniques, 20–30% of renal cancer patients have metastasis at the time of diagnosis, and 20–40% of patients who undergo nephrectomy for the treatment of RCC will develop distant metastasis³. Without treatment, the five-years survival rate in patients with metastatic RCC is less than 10%, and the average survival is 7–12 months⁴. Computed tomography (CT, MSCT) has an unreplaceable role in the follow-up of patients with high risk of metastasis. The aim of these methods is early detection of solitary metastasis that can be urgently surgically removed⁵. All three patients in this report were followed up after nephrectomy in accordance with the European Association of Urology (EAU) guidelines.

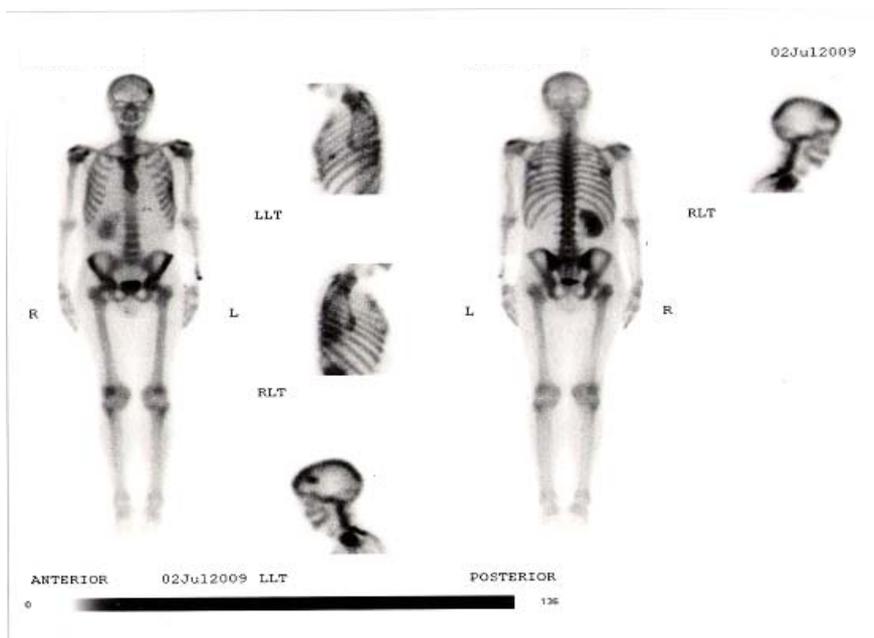


Fig. 9 – Bone scintigraphy detected left parieto-temporal bone metastasis.

Case 3

A 39-year-old man with the history of right radical nephrectomy for the stage G2, pT1, Nx, Mx RCC, who later required surgical removal of retroperitoneal RCC lymph nodes

RCC can give metastasis in the lymph nodes or any other organ, but the most frequent metastasis are discovered in the lungs, lymph nodes, liver, bone and adrenal gland⁵. Surgical removal of solitary metastasis is considered the best therapeutic option, and studies have shown that the five year

survival was up to 35% higher in patient who had surgery, compared to those who did not⁶. Today surgical removal of metastasis is frequently combined with tyrosin kinase inhibitors and "target" therapy, and this therapy may confer some benefit, and increase survival by several months.

Up to 3.3% of patients have lymph node involvement at the time of nephrectomy. These patients have poor prognosis. Some data suggest that lymph node dissection does not improve survival⁷, but one recent retrospective study from the USA on 900 patients showed that lymph node dissection may prolong survival by five months⁸. The first patient in our report had the evidence of paraortic lymph node RCC metastasis two years after nephrectomy, and was treated with surgery. The second patient initially underwent regional lymph node dissection and had no evidence of further lymph node involvement throughout the follow-up period. The third patient, soon after the nephrectomy, six months later, underwent regional paracaval lymph node dissection due to metastasis and the same operation was repeated on two other occasions in the next two years.

Patients with solitary surgically resectable RCC pulmonary metastasis have better prognosis than patients with metastasis in other organs, and a five-year survival rate after lung metastasectomy is up to 54%⁹. A five-year survival of patients with complete resection of multiple pulmonary metastasis is up to 29%. Immunotherapy with interferon-alpha in cases of metastatic disease involving the lungs is beneficial for a small number of patients 7–15%¹⁰. RCC develops from the proximal tubules who have a high level of P-glycoprotein expression that leads to resistance for known types of chemotherapy. Chemotherapy with 5-fluorouracil has better results if combined with interferon immunotherapy; this is the treatment offered, in accordance to EAU protocols, to the second patient in this report and resulted in regression of lung metastasis and remission of the disease⁵. Temsirolimus has somewhat better results regarding survival in patients with metastatic RCC when administered as first line therapy⁵, and this is why it was used in our second patient.

Prognosis is poor in patients with bone metastasis, especially when metastasis involves the axial skeleton. A five-year survival is up to 38% in patients who undergo resection of solitary bone metastasis from the pelvis or limbs, but it is only 7% in patients with multiple bone metastasis¹¹. Similarly, data show that surgical treatment of solitary bone metastasis results in a prolonged survival and better quality of life¹². The second patient in our report did not have surgery

or therapy with bisphosphonates, after bone scan revealed metastasis to the skull, because of his poor general condition.

RCC metastasis in the gastrointestinal tract, excluding the liver, are rare, and are seen in 0.2–0.7% of patients¹³. Such metastatic lesions are most frequently localized in the pancreas, whereas RCC metastases in the stomach, small bowel or colon are very rare. All the three patients in our case report had RCC metastasis to the colon, and bowel resection was the only treatment option. Although gastrointestinal metastasis is rare, all the three reported patients had diagnostic workup of the abdomen, including colonoscopy because of gastrointestinal symptoms, such as abdominal pain, flatulence, diarrhea or constipation. Indeed, colonoscopy confirmed the presence of tumor metastasis in the colon in two patients. Although published data show that RCC metastatic lesions in the intestinal tract most frequently manifest as gastrointestinal bleeding or occlusion, that was not the case in our report. The third reported patient underwent immuno-chemotherapy, including interferon alpha and 5-fluorouracil, because the target therapy for metastatic RCC was not available at our hospital in 2007.

Cerebral RCC metastasis occurs in 4–10% of patients⁶. Radiotherapy has no effect on cerebral RCC metastasis, but surgical excision of solitary metastasis may prolong survival by 12.1 months on average¹⁴, whereas radiosurgery using the gamma knife may prolong survival by up to 15 months in selected cases¹⁵. In the second patient, surgical treatment for multifocal brain lesions was not possible, and radiotherapy of the metastases was not an option because cerebral RCC metastasis is resistant to radiation therapy.

RCC patients with nephrectomy need a prolonged follow-up, because delayed metastasis may occur even 20 years after nephrectomy. Surgical resection of metastatic lesions, especially solitary lesions, has a place, and a multidisciplinary approach gives the best results^{5,6}.

Conclusion

Early detection of organ RCC metastasis, while a lesion is still surgically treatable, and the surveillance of oncologic patients in accordance to the EAU guidelines, adjusted as needed to each individual patient, could provide good results. A multidisciplinary approach to the treatment is recommended in patients with metastatic RCC, since it might result in better quality of life and longer survival.

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Received on May 15, 2012.
Accepted on May 21, 2012.
OnLine-First March, 2013.