

Metastatic colorectal carcinoma and kidney tumors: a report of four cases

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ABSTRACT

Aims and background. The prognosis of patients with metastatic colorectal carcinoma (CRC) has improved substantially over the last two decades. Longer patient survival comes at a price of more complications, including second primary neoplasms and metastases at unusual sites.

Method. Retrospective chart review.

Results. We present 4 patients with metastatic CRC who developed kidney tumors. In 2 cases, partial nephrectomy or nephrectomy was performed for second primary renal cell carcinoma. The patients survived 2.5 and more than 6 years after kidney surgery. In the other 2 patients the kidney tumors were diagnosed as CRC metastases, histologically verified in one case; these two patients died within two years of diagnosis of kidney involvement.

Conclusion. The diagnostic approach to kidney tumors in CRC patients should include a biopsy because only patients with primary renal cell carcinoma and selected patients with metastatic CRC benefit from nephrectomy. Free full text available at www.tumorionline.it

Introduction

Metastatic colorectal carcinoma (CRC) is one of the most common malignant tumors in the Western world. The prognosis of patients with metastatic CRC has improved substantially over the last two decades with the advent of new cytotoxic drugs and, more recently, biological agents¹. The median survival of patients with metastatic CRC in most recently reported prospective trials is between 18 and 24 months, and, although only resection of liver or lung metastases offers a chance for cure, a substantial proportion of these patients survive more than 5 years. Longer patient survival comes at a price of more complications of therapy or disease itself. The natural history of the tumor may be revealed beyond what was known during the originally short median survival between 6 and 12 months. This natural history may include metastases at unusual sites as well as second primary neoplasms²⁻⁴.

Second primary neoplasms are common in cancer patients. They occur as a result of common risk factors (e.g., age, genetic predisposition or environment), as a result of cancer therapy, or simply by chance. Second primaries in patients without evidence of activity of the first primary tumor are usually managed according to the same principles as in patients without a history of cancer. On the other hand, in the case of the diagnosis of a second primary neoplasm in a patient with incurable metastatic cancer the physician faces a challenge. An optimal therapeutic strategy should be selected individually based on the knowledge of biology and therapeutic results in both tumors.

Renal cell carcinoma (RCC) is a tumor with a rapidly increasing incidence in some countries, including the Czech Republic. RCC is commonly associated with second

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primary neoplasms^{5,6}. It is characterized by a peculiar biological behavior with considerable variation in clinical course, including spontaneous regression of metastases or an indolent course of metastatic disease as well as rapidly fatal metastases, paraneoplastic syndromes and metastases at unusual sites⁷⁻⁹. Mutation or epigenetic changes in the von Hippel-Lindau gene, present in most cases of RCC¹⁰, result in increased production of vascular endothelial growth factor (VEGF), which could be responsible for some of the biological peculiarities of RCC. RCC is not uncommon as a second primary tumor in CRC^{2,5,6}. On the other hand, the kidney is an unusual site of metastases in CRC¹¹⁻¹⁴.

We present 4 patients with metastatic CRC and kidney tumors (Table 1), including histologically verified second primary RCC in two cases. Because treatment of metastatic CRC resulted in long-term disease control, nephrectomy was performed in the 2 patients with second primary RCC, and long-term survival was obtained in both cases.

Case descriptions

Patient 1

A 70-year-old man underwent sigmoid resection for carcinoma with synchronous liver metastases in December 2000. He was then treated with hepatic arterial infusion of the combination of irinotecan, 5-fluorouracil and leucovorin administered through a surgically implanted catheter. The treatment was continued until August 2002 and resulted in partial response of liver metastases and normalization of the originally increased serum carcinoembryonic antigen concentration. During a follow-up examination, a tumor in the left kidney was detected and nephrectomy was performed in October 2002. Chromophobe carcinoma was

evident on histological examination of the nephrectomy specimen. The patient was given regular follow-up. Progression of liver metastases was detected in the spring of 2005. The patient was treated with the combination of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX7) resulting in a partial response, and remained under observation afterwards. In June 2006, progression of liver metastases was evident. The patient was treated with the combination of cetuximab, irinotecan, 5-fluorouracil and leucovorin, resulting in a minor response. Because of poor tolerance, the treatment was terminated in December 2006. In February 2007 the patient underwent a liver resection, which was considered curative. Histological examination revealed metastasis of colon carcinoma. At the last follow-up visit in September 2009, more than 6 years after nephrectomy, the patient was alive without evidence of recurrence of either CRC or RCC.

Patient 2

A 66-year-old man with a history of hypertension and diabetes mellitus underwent resection of the rectosigmoid for carcinoma on April 5, 2001. Tumor stage was pT3N1M0. Four cycles of adjuvant therapy (5-fluorouracil and leucovorin) and radiation were administered postoperatively. Liver metastases were detected in November, 2002. The patient was referred to our center and underwent implantation of an arterial catheter with a subcutaneous port system into the hepatic artery on February 10, 2003. Arterial infusion of the combination of irinotecan, 5-fluorouracil and leucovorin was started in February 2003, and continued at weekly intervals until August, 2004. A tumor in the inferior pole of the right kidney was detected on a control CT scan. On September 16, 2004 the patient underwent resection of the right kidney. Histological examination revealed clear cell carcinoma. Progression of liver metastases was evident in

Table 1 - Characteristics of the patients

Patient	Age at diagnosis of CRC (years)	Therapy	Duration of metastatic CRC at the diagnosis of kidney tumor (months)	Procedure for kidney tumor	Histology	Subsequent therapy	Patient status	Survival after diagnosis of kidney tumor or nephrectomy (months)
1	70	HAI FOLFIRI	22	Nephrectomy	Chromophobe RCC	FOLFOX7; cetuximab + FOLFIRI	ANED	82
2	66	HAI FOLFIRI	22	Resection	Clear cell RCC	FOLFOX7; cetuximab + FOLFIRI; FOLFOX7	DOD	30
3	49	HAI FOLFIRI	23	Biopsy	Intestinal adenocarcinoma	FOLFOX7	DOD	9
4	69	FOLFIRI	0	Biopsy	Not diagnostic	FOLFIRI	DOD	24

ANED, alive, no evidence of disease; DOD, died of disease; CRC, colorectal carcinoma; RCC, renal cell carcinoma; FOLFIRI, leucovorin (folinic acid), 5-fluorouracil and irinotecan; FOLFOX, leucovorin (folinic acid), 5-fluorouracil and oxaliplatin; HAI, hepatic arterial infusion.

January 2005. The patient was treated with 8 cycles of the combination of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX7) resulting in stable disease and was subsequently followed. Progression of liver metastases was evident on control CT in October 2005. The patient was then treated with the combination of cetuximab, irinotecan, 5-fluorouracil and leucovorin, which resulted in a minor response and was continued until September 2006. Progression was observed on CT scan in October 2006. The patient was re-treated with FOLFOX7, but clinical and laboratory signs of progressive disease were evident after 4 cycles and the patient died on March 30, 2007. No autopsy was performed.

Patient 3

A 49-year-old man presented with intestinal obstruction and was treated with resection of a carcinoma of the splenic flexure on October 1, 1998. Tumor stage was pT2N0M0. Six cycles of adjuvant chemotherapy (5-fluorouracil and leucovorin) were administered. Multiple liver metastases were detected and an arterial catheter with a subcutaneous port system was introduced into the hepatic artery in December 1999. The patient was treated with arterial infusion of irinotecan, 5-fluorouracil and leucovorin at weekly administration until November 2000, which resulted in a partial response. Hepatic arterial infusion of interferon-alpha (10 MU 3 times weekly) was administered as consolidation therapy from January through March 2001. The patient then remained under observation. He received systemic combination therapy including irinotecan, 5-fluorouracil and leucovorin for progression of liver metastases from December 2001. Along with progression of liver metastases, a tumor in the right kidney was evident on control CT scan in November 2002. Biopsy demonstrated metastasis of adenocarcinoma. The patient was subsequently treated with the combination of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX7). He died on August 24, 2003. No autopsy was performed.

Patient 4

A 69-year-old man presented with intestinal obstruction that was treated with subtotal colectomy on October 28, 1999 for adenocarcinoma of the descending colon (pT3N1M0). The postoperative course was complicated by hemorrhage requiring surgical revision with splenectomy. Subsequently, the patient was treated with adjuvant combination chemotherapy including 5-fluorouracil and leucovorin. In January 2002 multiple liver metastases and a tumor in the left kidney infiltrating the back muscles and pancreas were detected on CT scan. The tumor of the kidney did not have the typical appearance of RCC. Nevertheless, a percutaneous biopsy was indicated that was, however, not diagnostic. Because of the presentation (history of advanced carcinoma of left colon with surgical complications and simultaneous multiple liver metas-

tases) and radiological appearance, repeat biopsy was not requested. Moreover, the tumor of the kidney was of borderline operability, and in the presence of multiple liver metastases the surgery would not be radical. The patient was treated with systemic combination therapy including irinotecan, 5-fluorouracil and leucovorin. On control CT scan in November 2002, the kidney tumor was stable while minor progression of the liver metastases was observed. The patient was subsequently treated with capecitabine. The disease progressed slowly, and because of the general condition of the patient only symptomatic therapy was provided. The patient died on February 14, 2004. No autopsy was performed.

Discussion

Our findings suggest that nephrectomy or partial nephrectomy may be beneficial in selected patients with metastatic CRC and second primary RCC. The benefit of nephrectomy in patients with metastatic RCC has long been considered controversial, but data from retrospective¹⁵ and randomized prospective studies^{16,17} now demonstrate that nephrectomy is associated with a survival benefit in patients with metastatic RCC treated with cytokines. It is evident that nephrectomy has an effect on distant metastases, as has been suggested earlier by rare observations of "spontaneous" regression of metastases after nephrectomy¹⁸. The mechanism of the suppressive effect of nephrectomy on the growth of distant metastases is unclear. It is now evident that RCC produces high quantities of VEGF. Neutralization of VEGF by administration of a monoclonal antibody is effective in metastatic RCC¹⁹, and nephrectomy probably exerts its antitumor effect, at least partly, by elimination of the source of endogenous VEGF. Anti-VEGF therapy is also effective in patients with metastatic CRC both in the first and second-line setting^{20,21}.

Kidney metastases are rare in CRC¹¹⁻¹⁴, but may be generally associated with an unfavorable prognosis. Patients with metastatic CRC and kidney tumors therefore present a diagnostic and therapeutic challenge. Biopsy of the kidney tumor should be performed in patients in good condition with a limited extent of CRC metastases responsive to therapy to distinguish between CRC renal metastasis and second primary RCC. The history of neoplastic disease could also be helpful in some cases. Systemic chemotherapy is the treatment of choice for CRC renal metastases, and, except for rare emergencies or cases with resectable disease, nephrectomy has no role in the management of CRC renal metastases. In case of inconclusive biopsy results, management should be based on radiological and clinical findings, as in one of the patients in the present series.

In second primary RCC in patients with metastatic CRC the choice of therapy may be more difficult. Nephrectomy or partial nephrectomy is clearly indicat-

ed in patients with early-stage CRC and second primary RCC²². Nephrectomy or partial nephrectomy is also currently the standard of care in patients with RCC and synchronous metastases who have a good performance status and are candidates for therapy with biological agents. The indication for nephrectomy in patients with suspected RCC and metastases originating from other primary tumors should take into account the prognosis of the metastatic tumor, the patient's performance status, the presence of comorbid disorders, and the possibilities for further therapeutic interventions for metastatic disease. It cannot be excluded that the removal of RCC might favorably influence metastases of other primaries, possibly through an anti-VEGF mechanism, but the rarity of such situations precludes any systematic analysis. The decision whether or not to perform nephrectomy should be made on an individual basis, after discussion with the patient. Because of the improvement of the prognosis of metastatic CRC associated with the advent of new therapeutic agents, an active approach in the treatment of second primary RCC that involves nephrectomy may be beneficial. Because of the rarity of this situation, there are no prospective data and only case reports like the two cases described here may help the physician in selecting the appropriate treatment.

In conclusion, selected patients with metastatic CRC and second primary RCC may benefit from nephrectomy. Systemic chemotherapy is the treatment of choice in patients with CRC metastases to the kidney.

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