



Durable remission of inoperable liver metastasis from rectal cancer after hepatic arterial infusion of oxaliplatin and 5-fluorouracil in combination with intravenous cetuximab

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ABSTRACT

At diagnosis of a cT3N0M1 adenocarcinoma of the rectum with synchronous inoperable liver metastases, a 59-year-old man was treated with preoperative radiotherapy (5×5 Gy), followed by laparoscopy-assisted anterior resection of the rectum with total mesorectal excision. At the first postoperative evaluation, a new lung metastasis was detected. First-line chemotherapy with FOLFIRI (5-fluorouracil, irinotecan, leucovorin) resulted in transient stabilization of the metastatic liver disease. At progression, oxaliplatin and 5-fluorouracil–folinic acid were administered by intrahepatic arterial infusion, in combination with intravenous cetuximab. A partial radiologic response was obtained, with complete metabolic response on fluorodeoxyglucose positron-emission tomography, and normalization of carcinoembryonic antigen values. The solitary lung metastasis was sequentially treated with radiotherapy and resection. Five years after the initial diagnosis, this patient remains free from progression, with residual cystic remnants of the liver metastases visible on conventional computed tomography imaging, but not enhancing with fluorodeoxyglucose positron-emission tomography.

KEY WORDS

Hepatic arterial infusion, colorectal, liver metastases, cetuximab, oxaliplatin, remission

1. INTRODUCTION

Each year, more than 5000 new cases of colorectal cancer (CRC) are diagnosed in Belgium, and 412,900 in the European Union overall. Those numbers represent an estimated incidence rate of 53.3 (for men) and 34.3 (for women) per 100,000 in a Belgian population of about 10 million inhabitants¹. About half of all patients diagnosed with CRC will develop liver metastasis (LM) during the course of their disease. In half of those patients, the LM will already be detectable at

the time of the initial diagnosis². The mean adjusted 5-year relative survival for patients diagnosed with CRC is 53.8% according to the EUROCARE project³. The survival rate for patients diagnosed with stage IV disease is much worse, with a 5-year overall survival of 5.7%⁴. However, among patients with stage IV CRC and metastases limited to the liver that are amenable to surgical R0 resection, the 5-year overall survival ranges between 17% and 25%⁵. Contemporary combination chemotherapy regimens, potentially combined with agents targeted to vascular endothelial growth factor (VEGF) or epithelial growth factor receptor (EGFR), permit initially inoperable patients to be reconsidered for resection of LM after regression of the metastases. Survival rates are comparable to those seen in patients with upfront resectable LM. A cure rate of 16% has recently been reported in this setting⁶. Furthermore, adjuvant systemic therapy after hepatectomy may contribute to improved survival^{7,8}.

Despite improvements in the activity of combination chemotherapy and of combinations with VEGF- or EGFR-targeted therapeutics, nearly all patients who are diagnosed with extrahepatic metastases or with inoperable LM cannot be offered cure and long-term disease control. Hence, 5-year survival rates remain disappointingly low in this patient population. The median overall survival rates observed in the experimental arms of two recently conducted phase III trials, with the FOLFIRI [5-fluorouracil (5FU), irinotecan, leucovorin] plus cetuximab regimen, or the FOLFOX (5FU, leucovorin, oxaliplatin) plus bevacizumab combination, were 24.9% (wild-type *KRAS* patients only) and 21.3% respectively^{9,10}.

A long-pursued treatment strategy to improve the outcome of patients with inoperable CRC metastases confined to the liver has been the use of regional chemotherapy by hepatic arterial infusion (HAI) of cytotoxic agents such as floxuridine, 5FU, oxaliplatin, or irinotecan^{11–13}. This approach has resulted in encouraging tumour response rates within the liver. In patients with unresectable CRC LM, the use of single-agent cytotoxic therapy with a fluoropyrimidine by

HAI compared with the systemic route of administration did not unequivocally demonstrate superiority in terms of survival¹⁴. In the neoadjuvant setting, compared with systemic administration, HAI did result in superior survival (24.4 months vs. 20 months, $p = 0.0034$)¹¹, with better physical function.

Several recently reported phase I/II protocols have tested the feasibility and effectiveness of integrating HAI into new combination therapies of cytotoxic drugs. We recently reported the feasibility of combining the EGFR-targeted monoclonal antibody cetuximab with combination chemotherapy by HAI¹⁵. Here, we report the case of 1 patient treated in that phase I study who experienced an unexpected durable remission after combined-modality treatment involving HAI for synchronous inoperable LMS and a solitary lung metastasis of a rectal adenocarcinoma.

2. CASE REPORT

A 59-year-old man underwent colonoscopy in February 2004 because of a history of tenesmus and change in defecation habits for 4 weeks. A circumferential stenosing rectal tumour was diagnosed at 12 cm above the anal verge. Biopsy revealed an adenocarcinoma of the rectum (*KRAS* wild type). Physical examination and laboratory data were within normal ranges, except for carcinoembryonic antigen, which was 11.3 µg/L (normal range: 0–3.0 µg/L).

Computed tomography (CT) of the abdomen and magnetic resonance imaging of the liver revealed 2 LMS distributed in both lobes with a maximum diameter of 14 mm.

In March 2004, after preoperative radiotherapy (5×5 Gy), the primary tumour was resected (laparoscopy-assisted anterior resection with total mesorectal excision and coloanal anastomosis with protective ileostomy). Pathology staging indicated a moderately differentiated adenocarcinoma with 17 examined lymph nodes all free of metastasis (pT3N0M1). Four months after the surgical intervention, progression of the LMS and a solitary lung metastasis to the upper right lobe were detected.

Systemic chemotherapy according to the FOLFIRI scheme (with modulated 48-hour continuous infusion of 5FU) was initiated. A best objective tumour response of stable disease (by the Response Evaluation Criteria in Solid Tumors) was obtained. After 1 year, the patient requested interruption of the chemotherapy because of increasing digestive intolerance. Two months later, progression of the lung metastasis was documented on CT imaging [Figure 1(A)].

In September 2005, a hepatic artery catheter was inserted during laparoscopy¹⁶. Treatment with cetuximab (400 mg/m² intravenously over 120 minutes for the first dose, and then 250 mg/m² intravenously over 60 minutes once weekly thereafter) was initiated in October 2005 in a phase I study, followed by HAI with oxaliplatin (100 mg/m² over 60 minutes), followed by

continuous HAI of 5FU modulated by 400 mg L-folinic acid administered intravenously¹⁵.

From the third cycle onward, oxaliplatin was administered intravenously because of HAI-related acute abdominal pain (grade 3).

At the first tumour evaluation, 8 weeks after initiation of treatment, a normalization of the level of carcinoembryonic antigen was documented in a blood analysis, as was a partial response, with regression of the LMS and lung metastasis on CT imaging [Figure 1(B)]. A best objective tumour response (partial response by the Response Evaluation Criteria in Solid Tumors) was obtained after 16 weeks of therapy, with normalization of the ¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG-PET) image, which together provided evidence for a complete metabolic response. Treatment was stopped at this point (end of March 2006) because of a progressive toxic interstitial pneumonitis (Figure 2). A colon re-anastomosis was then performed.

Reappearance of FDG-PET positivity of the lung metastasis, but not of the LMS, was observed in June 2006 [Figure 1(C)], after which that metastasis was treated by radiotherapy (highly conformal radiotherapy, 45 Gy in 6 fractions). Despite the radiotherapy, the lung metastasis progressed over the next few months. Meanwhile, the liver lesions maintained stable dimensions and remained FDG-PET-negative. In January 2007, a wedge resection of the right upper lung lobe was performed. The anatomopathology result revealed a lung metastasis of the rectal carcinoma with tumour-free cutting margins and pleura.

At the most recent follow-up in February 2010, 5 years after the initial diagnosis of CRC stage IV with inoperable LMS and lung metastasis, the patient remains free from progression of the rectal carcinoma, with stable cystic non-FDG-enhancing liver lesions still visible on CT imaging [Figure 1(D)].

3. DISCUSSION AND CONCLUSIONS

Patients with CRC LM have a poor survival prognosis when no R0 surgical resection of the LM can be offered¹⁷. In the present case, first-line chemotherapy (FOLFIRI¹⁸) could not force a durable remission. Shortly after interruption of that chemotherapy regimen, progression of disease occurred, including development of a lung metastasis. By contrast, second-line HAI reached a threshold of activity that obtained a durable remission of the LMS. However, the extrahepatic disease location progressed (indicating inferiority of the systemic exposure to the cytotoxic treatment), but could be salvaged with surgery. This case history offers “intra-patient” evidence of the higher activity in the liver of chemotherapy by HAI than by systemic therapy, with the efficacy of that activity exemplified by the lung metastasis result. A discrepancy between HAI and intravenous chemotherapy is a more plausible explanation than is

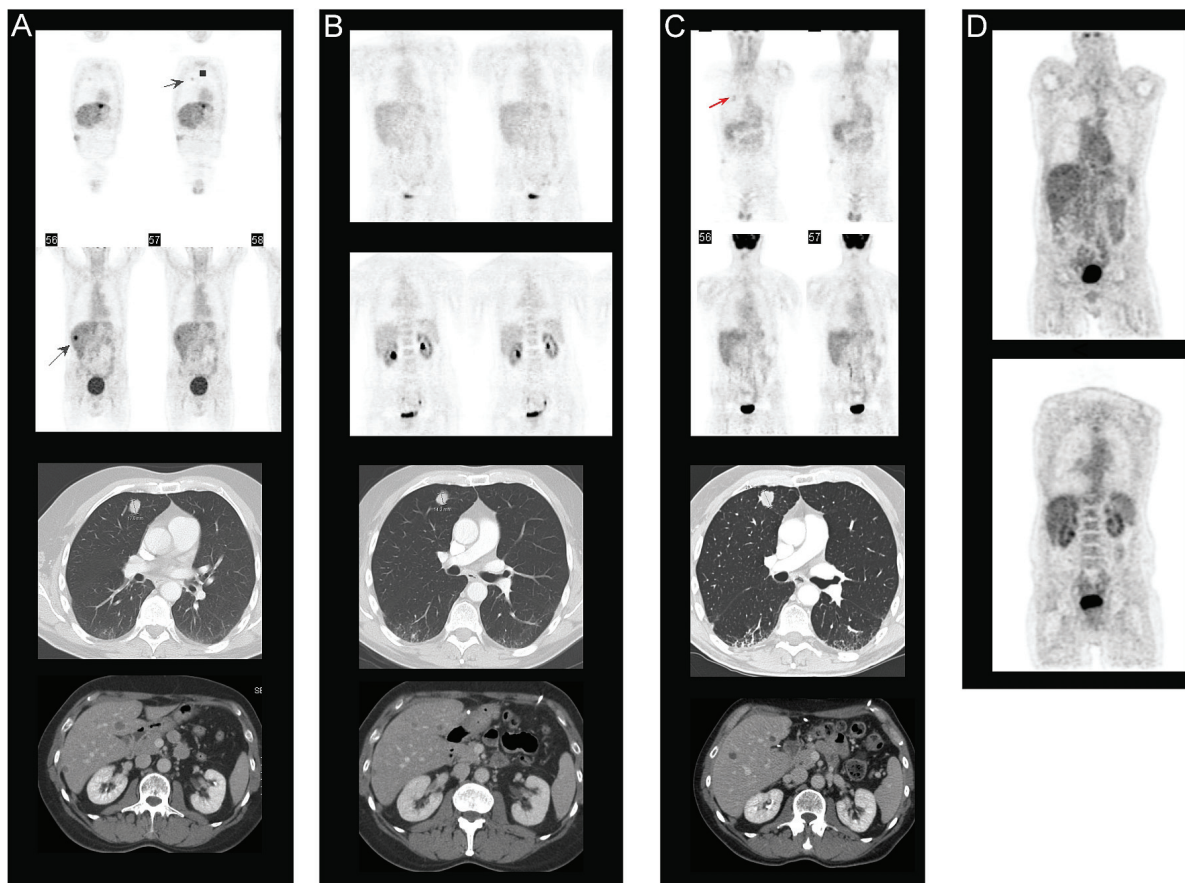


FIGURE 1 Chronology of disease evolution in the patient. (A) Assessment before start of intrahepatic arterial infusion (HAI): anterior radio-labelled fluorodeoxyglucose (FDG) positron-emission tomography (PET) images show FDG-positive bilobar liver metastases and a solitary lung metastasis (arrows). The corresponding computed tomography (CT) images of lung and liver are shown immediately below. (B) Assessment at the end of HAI, after a normalization of serum carcinoembryonic antigen: FDG-PET shows complete metabolic response. Corresponding CT images are shown immediately below. (C) Imaging by FDG-PET after reactivation of lung lesion and before conformal radiotherapy to treat progressive disease. Corresponding CT images of the liver show only leftover cystic lesions. (D) Most recent FDG-PET images reveal no FDG-positive lesions.

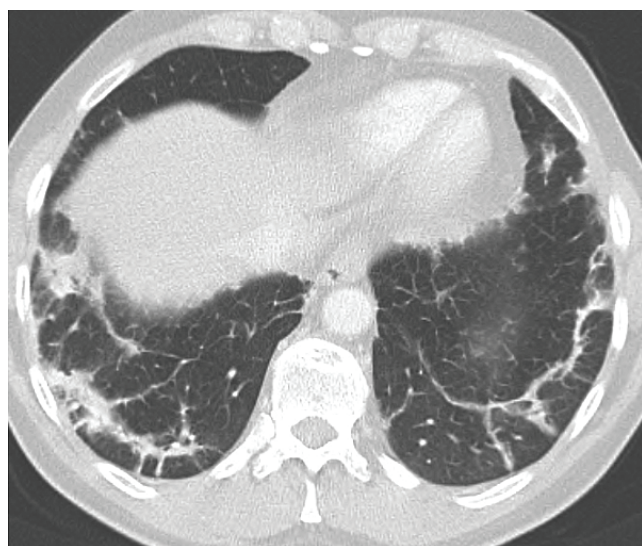


FIGURE 2 Adverse event: interstitial pneumonitis seen on computed tomography imaging.

a difference in chemosensitivity at the two sites of metastasis: durable complete response in one, compared with PET response followed by progressive disease in the other.

The durable remission in the liver with only remnants of non-FDG-enhancing cystic lesions remaining is the result of a profound cytoreduction in response to the combination of HAI chemotherapy (oxaliplatin–leucovorin–5FU) and intravenous EGFR inhibitor (cetuximab, a monoclonal antibody with demonstrated activity against wild-type *KRAS* CRC). Further investigation of combination therapy, including HAI such as that used in our case, can be a more promising treatment strategy for unresectable LM from CRC and deserves further study in a prospective phase II trial.

4. CONFLICT OF INTEREST DISCLOSURES

No author has any commercial association that might create a conflict of interest in connection with the present manuscript.

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