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Liver metastases of colorectal cancer — what are the limitations of multimodality treatment?

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ABSTRACT

The prognosis of patients with liver-only metastases of colorectal cancer varies significantly, depending mostly on technical resectability of metastases. Possible treatment modalities include surgical resection, methods of local ablative treatment, as well as systemic chemotherapy. Hereunder, we present a case of a 52-year-old male patient with colon cancer metastases limited initially to the liver, who underwent multimodality treatment consisting of systemic chemotherapy and several forms of localised treatment: radioembolisation, non-anatomical resection and thermoablation of liver metastases, and wedge resection of lung metastasis. Despite achieving long-lasting control of liver metastases, localised treatment resulted also in chronic thrombocytopenia, which prevented introduction of optimal subsequent systemic treatment.

Key words: colorectal cancer, metastases, radioisotope therapy, surgery, chemotherapy

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Introduction

Patients with colorectal cancer (CRC) with liver-only metastases have varied prognosis, which depends mostly on prognostic factors related to the cancer itself and on the technical possibility of implementing radical local treatment, mostly surgical resection [1]. Unfavourable prognostic factors related to cancer include: synchronous or metachronous type of developing metastases, disease-free survival time from primary resection, number and volume of metastases, and the presence or suspicion of extrahepatic metastases. Tools for risk evaluation that include prognostic factors, such as Fong score [2], allow estimation of the potential disease-free survival and provide guidance in selecting the most suitable candidates for surgical treatment.

Treatment of patients with initially resectable liver metastases consist mostly of surgical resection, which may or may not be supported by administration of systemic chemotherapy. Such a surgical-only approach results in five-year survival rates reaching nearly 50% [3]. The addition of perioperative chemotherapy, most com-

monly FOLFOX or CAPOX regimens, improve progression-free survival (PFS) without unequivocal statistical evidence for prolongation of overall survival [3]. Inclusion of currently available targeted therapies used in metastatic colorectal cancer into perioperative chemotherapy failed to improve long-term results [1]. In cases of liver-only metastases unambiguously unsuitable for radical treatment, even after achieving tumour response, the treatment of choice consists of palliative chemotherapy supported by methods of local and locoregional treatment when justified. Methods of local treatment applicable in such cases include: thermoablation [radiofrequency ablation (RFA) or microwave ablation] [4], stereotactic body radiotherapy (SBRT) [5], chemoembolization [6], or radioembolisation such as selective internal radiation therapy (SIRT) [7]. The major limitation of implementing local and locoregional methods in patients not suitable for radical treatment is insufficiency of good quality prospective data showing improvement in OS because most previously conducted studies have reported improvement in PFS only [8].

The subsequent group, which requires a different clinical approach, includes patients with initially unresectable liver metastases who might be candidates for radical treatment after achieving tumour regression. In most of those cases, systemic chemotherapy would be the treatment of choice, with or without addition of local ablative methods. No standard fit-for-all chemotherapy regimen have been established in this setting with similar uncertainties regarding role of targeted therapy. However, considering the correlation of response rate with rates of R0 resection, several combinations of chemotherapy with targeted therapies have been recommended. This includes the doublet of chemotherapy (FOLFOX/FOLFIRI) in conjunction with monoclonal antibody targeting epidermal growth factor receptor (EGFR), such as cetuximab, in patients without *RAS* gene family [9] as well as chemotherapy triplet (FOLFOXIRI) or doublet (FOLFOX/FOLFIRI) with monoclonal antibody targeting vascular endothelial growth factor (VEGF) bevacizumab in patients with verified *RAS* gene family mutation [10]. In clinical practice, selection of the right therapy remains difficult in most of the patients. An experienced multidisciplinary tumour board, consisting of an oncological surgeon (sometimes, depending on the clinical situation, this may also include a hepatobiliary surgeon and thoracic surgeon), medical oncologist, radiation oncologist, radiologist (in some cases also an interventional radiologist), and pathologist, should provide expertise and guidance in the most challenging cases. An appropriate combination of systemic, local, and locoregional therapy as well as development of convenient multidisciplinary cooperation may translate into substantial improvement of prognosis in patients with liver-only metastases from colorectal cancer. Nevertheless, complicated and multistage treatment carries the risk of additional adverse events, which in certain cases can constrict available treatment modalities. Hereunder, we report a case of a patient who, despite achieving impressive locoregional control of liver metastases, developed chronic toxicity that contraindicated further optimal systemic treatment.

Case report

A 52-year old patient, K. R., initially without any comorbidities, was diagnosed with colon cancer after pathological examination of a biopsy specimen taken during colonoscopy in July 2014. USG showed multiple, metachronous metastases in the liver, and this was confirmed in a CT scan of the abdomen performed on 21.07.2014, which demonstrated the presence of five liver lesions measuring from 18 to 54 mm. On 14.08.2014 the patient underwent laparoscopic resection of the sigmoid colon, and the pathology report confirmed the diagnosis

of colon cancer (adenocarcinoma tubulare G2, pT3 N1b, without confirmed mutations in *RAS* gene family). Due to the presence of multiple liver metastases, probably unresectable, the patient's treatment was qualified as palliative, and on 10.10.2014 a FOLFIRI chemotherapy regimen was initiated. After the first cycle the patient developed neutropaenia [grade 4 according to Common Terminology Criteria for Adverse Events (CTCAE)], which reoccurred on a regular basis during further treatment as grade 3 neutropaenia and required 20% reduction in chemotherapy doses, prolongation of intervals between chemotherapy cycles, and periodic support with granulocyte colony-stimulating factors. A CT scan taken after seven cycles of chemotherapy showed 13% regression in liver lesions (stable disease [SD], according to RECIST criteria). However, in a CT scan after 12 cycles liver tumours grew by 5%, which did not fulfil criteria for progression (Fig. 1A). At that time the patient was referred to a hepatobiliary surgeon, who qualified the liver metastases to be potentially resectable after achieving further regression. As initial chemotherapy with the FOLFIRI regimen showed moderate activity and simultaneously resulted in significant haematological toxicity, achieving further regression with chemotherapy escalation or regimen change seemed unlikely. After a discussion with the interventional radiologist, locoregional treatment with radioembolisation (SIRT) was proposed as a modality to induce regression of liver metastases. SIRT was performed on 09.07.2015, during an interval between chemotherapy cycles, without any complications (Fig. 2). A CT scan from 07.09.2015, taken after SIRT and 18 cycles of chemotherapy, showed a 19% reduction in the diameter of liver lesions (Fig. 1B). The response was confirmed on a PET-CT from 18.09.2015, which additionally excluded the presence of extrahepatic metastases. Therefore, the patient was qualified for two-stage surgical resection of liver metastases. Systemic treatment was withheld in October 2015 after 21 cycles of FOLFIRI. On 11.12.2015 the patient underwent the first stage of surgical treatment: non-anatomical resection of liver metastases within the left lobe of the liver and right portal vein ligation to induce hypertrophy of liver remnants. Unfortunately, the procedure resulted in occurrence of a vast haematoma within the left lobe of the liver (about 30–40% of the lobe volume) and no sign of liver remnant hypertrophy was seen during follow-up. Therefore, the second stage of surgical treatment had to be abandoned due to high risk of postsurgical liver failure. The next CT scan taken on 15.01.2016 showed additional regression of metastases left within the right lobe of the liver after the surgical procedure. The obtained reduction in lesion diameter reached 31%, which corresponded to partial response (PR) according to RECIST criteria (Fig. 1C). Regarding achieved disease control and

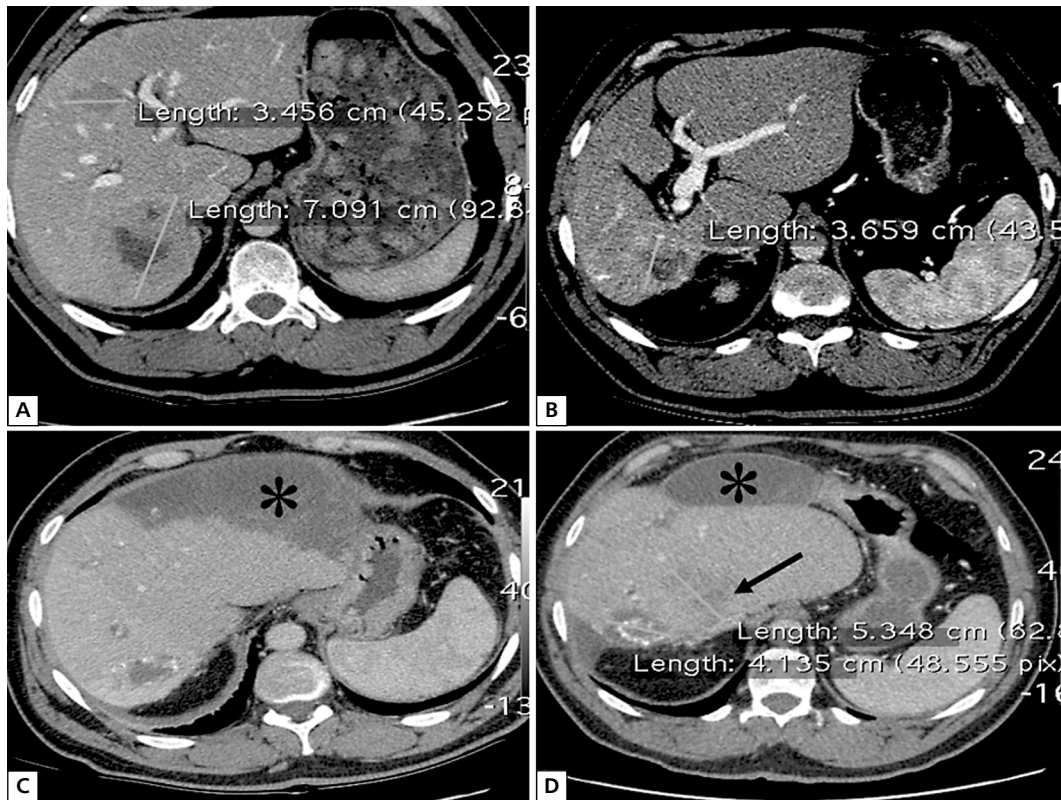


Figure 1. CT images showing changes in liver metastases: A — scan before radioembolisation; B — scan 2 months after radioembolisation; C — scan 4 months after radioembolisation and after resection of metastasis from left lobe of liver (*marks post-surgical haematoma); D — scan 2 years after radioembolisation (*marks residuary fluid collection from haematoma, arrow indicates presence of new metastasis)

previous toxicity of systemic treatment, the decision about withholding chemotherapy was sustained and the patient was only under follow-up. Disease progression was detected after a PET-CT performed on 31.05.2016 showed a metabolically active 10-mm lesion in the third segment of the left lung — progression-free survival (PFS) was 10.9 months since carrying out the SIRT procedure and 19.9 months since introduction of FOLFIRI chemotherapy. However, the liver lesion left within the right lobe of the liver continued to decline. Despite the suggestion of local treatment of lung metastasis, the patient decided to continue further follow-up only. A CT scan from 16.11.2016 confirmed growth of the lung lesion (now 13 mm) as well as the presence of a new lesion in the liver 12 mm in diameter, which resulted in liver-only PFS of 16.5 months since SIRT procedure. At this point, a chronic decrease of platelet count to about $100\text{-}150 \times 10^9/\text{L}$ was observed for the first time. The patient was offered second-line chemotherapy with FOLFOX4 + bevacizumab, but he decided to attempt radical treatment for both lung and liver metastases. On 01.02.2017 transabdominal USG-guided thermoablation of the liver lesion was

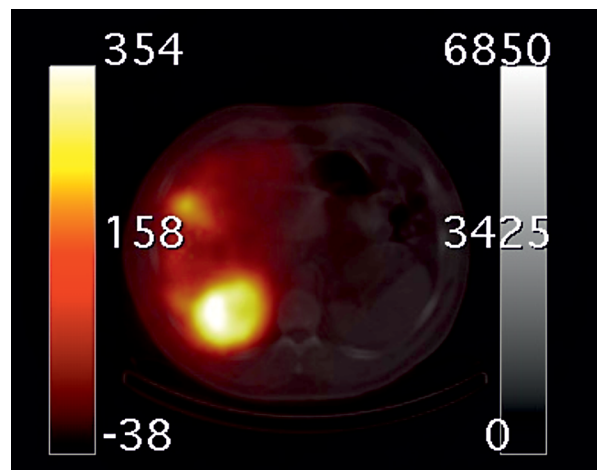


Figure 2. SPECT/CT imaging after intra-arterial administration of yttrium-90 resin microspheres showing acquisition of radiation within liver metastases

performed, and on 20.03.2017 wedge resection of the lung metastasis was carried out. However, a subsequent CT scan from 05.04.2017 revealed further progression

of the liver lesion to 51 mm, without the possibility of subsequent localised treatment (Fig. 1D). Although the patient agreed to start second-line chemotherapy, laboratory results confirmed chronic thrombocytopenia (grade 2 CTCAE) $50\text{--}100 \times 10^9/\text{L}$, unresponsive to a short-course of steroids.

Etiopathogenesis of thrombocytopenia remained unclear — according to the consulting haematologist, the presence of thrombopoietic suppressive factors secreted by neoplasm might be responsible, but sequestration of platelets in the disturbed vascular system of liver remnants may also occur. Chronic thrombocytopenia excluded the patient from the National Health Fund (NFZ) program of bevacizumab access in second-line treatment of CRC and prevented further access to panitumumab/cetuximab NFZ programs. Since 21.04.2017 the patient has received FOLFOX4 chemotherapy with 20% dose reduction and prolongation of cycle intervals because it allows us to conduct treatment without hazardous falls of the platelet count below $50 \times 10^9/\text{L}$. In the first CT scan obtained after FOLFOX4 introduction, the dimension of measurable lesions declined by 6%, including the previously fast-progressing liver lesion. The achieved stabilisation provides hope for gaining control over the disease. This would allow further prolongation of the patient's overall survival, which has currently reached nearly 35 months since first-line chemotherapy introduction.

Discussion

The presented case clearly shows how complex and peculiar modern CRC management can be. The development of, and growing access to, novel methods of local and locoregional treatment, as well as the combination of those methods with systemic treatment, can be used to provide tailored treatment that addresses the needs of each patient individually. However, this may come at the price of increased toxicities that complicate subsequent management. In the presented patient, treatment with SIRT provided long-term disease control in the liver (16.5 months), despite earlier extrahepatic progression (10.9 months). The finding comes along with the results of the SIRFLOX trial [7], in which a combination of radioembolisation with systemic chemotherapy, compared to systemic chemotherapy alone, prolonged liver-only median PFS (20.5 vs. 12.6 months, respectively) without any effect on global median PFS (10.7 vs. 10.2 months, respectively). It should be emphasised that in the presented case neither of the liver lesions covered with the SIRT procedure have yet progressed (during a period of 25.2 months). The effects of other implemented modalities on the fate of the discussed patient are more difficult to weigh up. The surgical approach, despite the

inability to carry out both stages of the procedure, had the potential to radically resect all present metastases, a factor known to improve prognosis [1]. Extra consideration should be given to the possibility of interaction between SIRT, which involves embolisation of hepatic arteries using yttrium-90 resin microspheres, and right portal vein ligation — because alteration of both arteries and veins of the hepatic vascular system could block sufficient liver hypertrophy. In terms of thermoablation, a successful procedure could radically ablate the source of local progression and postpone the need for systemic treatment, especially if we consider that no other lesion appeared during further follow-up. However, because the liver metastasis progressed immediately in the next CT scan, it may indicate that thermoablation under USG guidance missed the targeted lesion, and therefore commencing second-line chemotherapy was required. Value of wedge resection of lung metastasis and its timing remain unclear, particularly considering the low volume and slow growth dynamics of the lesion. Long-term toxicity, thrombocytopenia, attributed to the used techniques of local and locoregional treatment, was not significant from a clinical perspective. Nevertheless, due to the strict criteria of NFZ drug reimbursement, thrombocytopenia disqualified the patient from access to targeted therapies with a proven positive effect on overall survival (bevacizumab in second-line treatment and cetuximab/panitumumab in subsequent lines). The question of whether the benefit that the presented patient derived from locoregional treatment outweighs the loss from suboptimal systemic treatment, remains open. Overall survival for the patient from the initiation of chemotherapy reached 34.3 months and is ongoing. This significantly exceeded the median OS achieved in clinical trials assessing not only first-line treatment with FOLFIRI regimen itself (20.6 months in GERCOR trial [11]), but also median OS obtained with a combination of FOLFIRI with targeted therapies (28.7 months for FOLFIRI with cetuximab and 25 months for FOLFIRI with bevacizumab, both results from the FIRE-3 trial [12]). Another open issue involves quality of life — long-term local control secured with SIRT procedure allowed the patient to remain without systemic treatment and its negative burden for nearly 18 months. During this period, he remained asymptomatic and able to maintain a full-time job. The complicated fortunes of the presented patient are an explicit example on how modern management of CRC require multidisciplinary collaboration. Only rigorous partnership between different medical specialists allows the proper combination of different modalities to be chosen, in proper patients and in proper time. In the end, only strict collaboration can enable the full potential that lies within multimodality treatment and translate this potential into real clinical benefit for patients with CRC.

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