Management of brain metastasis from rectal cancer using whole-brain radiation therapy followed by bevacizumab and chemotherapy: A case report

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Abstract. Brain metastases in colorectal cancer are uncommon, which has resulted in a shortage of data concerning their screening and management. Multiple therapeutic modalities with chemotherapy, chemoradiation and targeted therapy, including bevacizumab and cetuximab regimens, have shown promising results. The present study describes the case of a 47-year-old male, diagnosed with T4N2M1 rectal cancer who underwent systemic therapy with modified FOLFOXIRI and cetuximab. The patient achieved a complete clinical response after 12 cycles. Following the discontinuation of cetuximab, the patient was given capecitabine as a maintenance therapy and subsequently developed brain metastasis. The patient received whole-brain radiation therapy (WBRT) followed by a bevacizumab plus FOLFIRI regimen. The patient showed a good response as revealed by cranial magnetic resonance imaging, with a reduction in lesion size and no sign of cerebral edema. In addition, the patient maintained a stable neurological condition for >10 months. These findings suggest that the early detection of brain metastases requires the close monitoring of neurological symptoms. In addition, WBRT followed by bevacizumab and chemotherapy is a potential management plan for brain metastasis from rectal cancer.

Introduction

Colorectal cancer is one of the most common types of malignant tumors worldwide. According to GLOBOCAN 2020 estimates (https://gco.iarc.fr/), colorectal cancer is the third most-diagnosed malignancy and the second leading cause of cancer-associated death. Regarding the pattern of metastasis in colorectal cancer, any organ can be a site of metastasis, including bone, the brain and distant lymph nodes, with the liver, lung and peritoneum being the most common sites (1). The incidence of brain metastases from colorectal carcinoma ranges from 0.06-4% and is more frequently seen in cases of rectal cancer (1,2).

Even though the prognosis of colorectal cancer is frequently poor with a median overall survival (OS) of 5-6 months, the survival time may be extended with combination treatment methods (3,4). The current therapeutic algorithm for metastatic colorectal cancer (mCRC) management from the National Comprehensive Cancer Network (5) and European Society For Medical Oncology (6) may involve a combination of different therapies which are tailored to the individual, based on the type and timing of prior therapy and the toxicity profiles of essential drugs. The main treatment approach includes systemic therapy and radical resection, if possible, often in conjunction with the local treatment of primary and metastatic sites. Regarding the increasing importance of targeted therapy in the treatment of mCRC, the mutational profile of the tumor is the focus of considerable attention. Evaluation of the KRAS/NRAS and BRAF mutation status, as well as HER2 amplifications and microsatellite instability/mismatch repair status are recommended for patients with mCRC (5). In addition to systemic therapy, locally ablative procedures or resection may be considered in cases of liver or lung oligometastases (6). However, as brain metastases are rare, there is a lack of data concerning the detection and management of this type of metastasis. In the present article, a case of a metachronous brain metastasis from rectal cancer treated using a multidisciplinary approach is reported.

Case report

A 47-year-old male with no previous medical history was admitted to Hanoi Medical University Hospital (Hanoi, Vietnam) in May 2021 with increasing constipation and a palpable inguinal lymph node. A colonoscopy showed a large serrated-ulcerative tumor in the lower rectum and anal canal, protruding by more than half of the bowel circumference.

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A biopsy of the mass revealed that it comprised adenocarcinomatous tissue. A metastatic inguinal node was confirmed via fine needle aspiration. On pelvic magnetic resonance imaging (MRI), it was observed that the tumor invaded the internal anal sphincter and levator ani muscle. In addition, malignant lymph nodes were detected around the bilateral iliac vessels, pelvic area and abdominal aorta, with irregular borders and enlarged sizes of 15x18 mm. The patient also received a cranial MRI and a computed tomography scan of the thorax and abdomen, which did not show any suspected metastasis sites (data not shown). Therefore, a diagnosis of stage T4N2M1 lower rectal cancer was made.

As the genetic test result of the patient ruled out RAS and BRAF mutations (test performed by Gene Solutions), the patient was given a modified FOLFOXIRI regimen comprising 150 mg/m^2 irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin and 2,400 mg/m^2 fluorouracil as a 48-h continuous infusion starting on day 1, every 2 weeks, with cetuximab at an initial dose of 400 mg/m^2, then 250 mg/m^2 weekly, as an initial treatment for 12 cycles, which ended in January 2022. The full sequencing data of the patient are not publicly available due to patient privacy. Imaging by cranial MRI, computed tomography of the thorax and abdomen, as well as ultrasound for peripheral lymph nodes, showed a complete clinical response, with lymph nodes measuring <10 mm on the short axis and lesions in the rectum appearing as flat white scars. At that time, the patient wished to discontinue the original regimen due to the adverse effects of the systemic treatment, which included anorexia and an intolerable cetuximab-induced rash, along with the increasing financial burden of the therapy. Therefore, it was decided to use capecitabine in a maintenance setting at a dose of 1,250 mg/m^2 twice a day from days 1-14, every 3 weeks. After two cycles of capecitabine, the patient developed a headache and mild paralysis. Cranial MRI revealed scattered nodules in the bilateral brain parenchyma, mostly in the grey-white matter border, hypo-intensity on T1-weighted imaging, hyper-intensity on T2-weighted imaging, slightly restricted diffusion on diffusion-weighted imaging, margin enhancement after contrast and extensive cerebral edema (Figs. 1 and 2). Following the elimination of all other possible causes, such as neurological infection or stroke, a diagnosis of rectal cancer brain metastasis was made. The patient was then given whole-brain radiation therapy (WBRT) with 30 Gy in 10 fractions.

After radiation therapy, the patient was reluctant to restart infusional treatment, so was treated with the aforementioned capecitabine regimen for three cycles. However, after experiencing little to no improvement of the persistent headache, the patient consented to a FOLFIRI and bevacizumab regimen comprising 5 mg/kg bevacizumab, 400 mg/m^2 fluorouracil intravenous bolus, 400 mg/m^2 folinic acid, 180 mg/m^2 irinotecan and 2,400 mg/m^2 fluorouracil as a 46-h continuous infusion starting on day 1, every 2 weeks. This neurological symptom subsided after two cycles. The cranial MRI of the patient performed in September 2022 after 6 cycles of the FOLFIRI bevacizumab regimen indicated a good response of the brain metastasis with a decreased lesion size and no sign of cerebral edema (Figs. 3 and 4). As of March 2023, the administration of the FOLFIRI plus bevacizumab regimen to the patient was continuing without adverse events. At this time, the patient had been living with brain metastasis for >10 months and maintained a stable neurological condition.

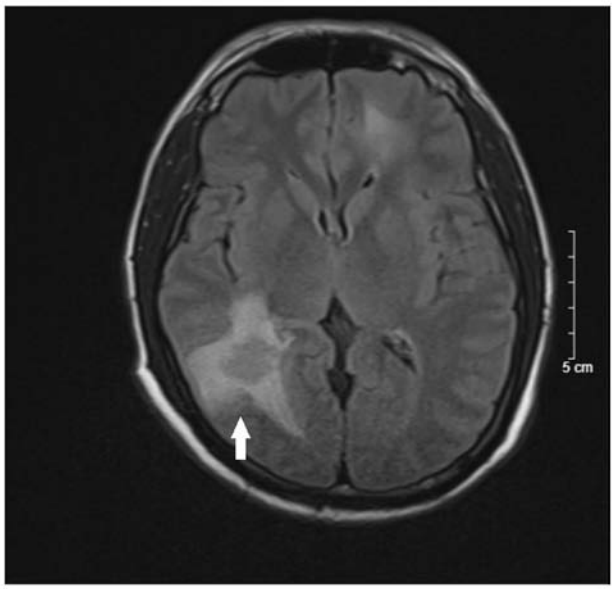

Figure 1. Cranial magnetic resonance image in March 2022 shows the lesion (white arrow) and extensive edema.

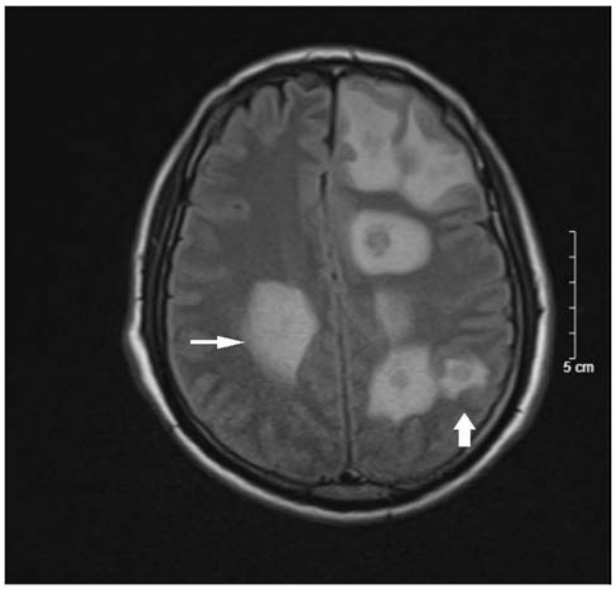

Figure 2. Cranial magnetic resonance image in March 2022 shows scattered nodules (white arrow) and cerebral edema (thin white arrow).

Discussion

Due to limited data on colorectal cancer metastases to the brain, the management of this remains a challenge for oncologists. Brain metastases are usually found in late-stage advanced diseases, and the vast majority of patients also have metastases at other sites (2). The incidence of brain metastases in mCRC is 14.6%, of which 76% of cases are asymptomatic (7). In the present case, nervous system imaging was indicated only after the patient presented with suspected neurological symptoms. Risk factors associated with brain metastases in patients

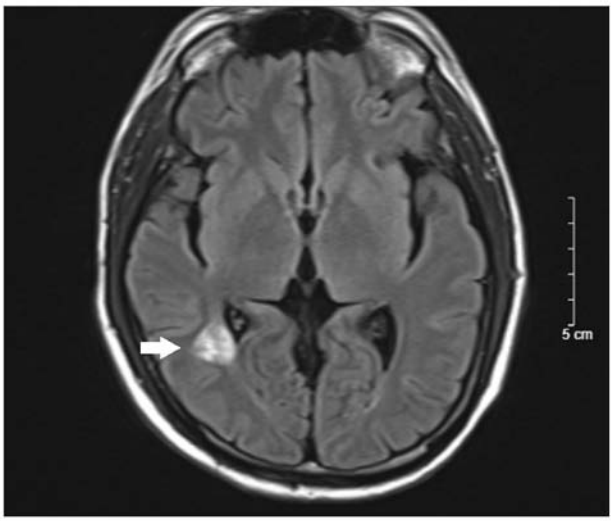

Figure 3. Cranial magnetic resonance image in September 2022 reveals that the lesion (white arrow) had decreased in size.

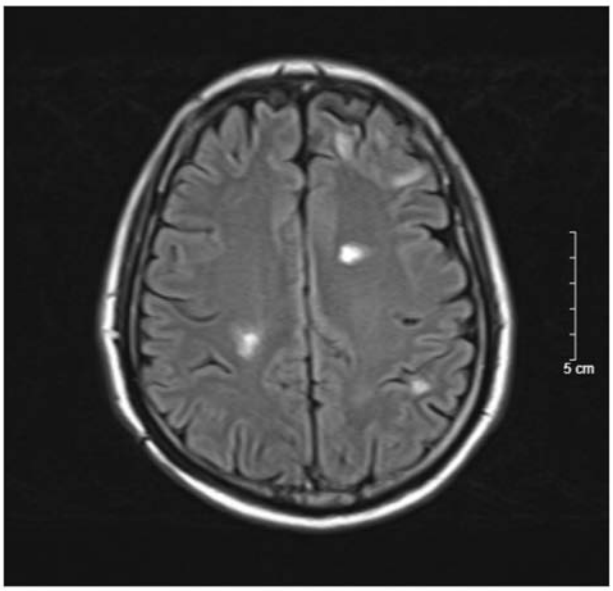

Figure 4. Cranial MRI magnetic resonance image in September 2022 exhibits no sign of cerebral edema.

with colorectal cancer have been noted in certain studies, which include a RAS mutation and concomitant metastasis in the lung and liver (3,8). However, none of these aspects was observed in the present patient.

For initial management, the FOLFOXIRI triplet regimen was selected because it has substantial efficacy in metastatic disease (9). The potential of adding cetuximab to the treatment plan was demonstrated in the FIRE-3 trial, and the doses used in the trial were applied to the present patient (10). However, exposure to all three active cytotoxic agents (irinotecan, oxaliplatin and fluorouracil) might be associated with a risk of increased toxicity. The original FOLFOXIRI regimen comprising 165 mg/m^2 irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin and 3,200 mg/m^2 fluorouracil as a 48-h continuous infusion starting on day 1 and administered every 2 weeks, has been reported to cause a higher rate of grade 3 and 4 neutropenia compared with the FOLFIRI combination (9). A modified FOLFOXIRI regimen has been shown to have more favorable efficacy and safety than FOLFOXIRI at the original doses (11). Despite receiving the modified regimen, the present patient experienced persistent anorexia and a cetuximab-induced rash during treatment.

The discontinuation of cetuximab may be a factor leading to brain metastasis in the present patient. The efficacy and safety of cetuximab as a maintenance therapy in patients following the effective completion of chemotherapy have been evaluated in the literature. For example, in one study cetuximab maintenance therapy significantly improved the median progression free survival (mPFS) of patients with mCRC to 11.6 months compared with 6.1 months in the observation group (12). However, capecitabine is also a standard treatment in mCRC. Despite the lack of head-to-head comparisons between the two regimens as subsequent therapy, capecitabine has been reported to lead to an mPFS of ~6.43 months, which is lower than that of cetuximab (13). Nonetheless, there is no known characteristic, feature or factor that is able to predict the likelihood of brain metastases; therefore, clinicians are prompted to take neurological signs into account at re-evaluation.

The standard approaches to brain metastases treatment include surgery, stereotactic radiosurgery and WBRT, either alone or in combination. In general, surgical resection is performed for a single large brain metastasis with massive edema or when the metastasis is in the eloquent brain area. Stereotactic radiosurgery is usually indicated for oligometastases, whereas WBRT is selected for patients who have multiple metastases or large-sized oligometastases with uncontrolled extracranial metastases, or who have a poor performance status (14). Patients with symptomatic brain metastases are recommended to be offered local therapy, comprising radiosurgery or radiation therapy plus surgery, according to the American Society of Clinical Oncology-Society for Neuro-Oncology-American Society for Radiation Oncology guidelines, regardless of the systemic therapy used for the systemic disease (14). For that reason, WBRT is a suitable choice for the present patient. The effectiveness of WBRT in the relief of symptoms and improvement of OS has been found in previous studies, with a median OS of 2-9 months (2,15). Koo *et al* (16) noted several risk factors associated with a poor prognosis, including older age (>65 years), multiple brain lesions (≥3), an elevated level of carcinoembryonic antigen (>5 ng/ml) at brain metastasis diagnosis, and extracranial metastases.

Evidence of the benefit of systemic therapy in patients with brain metastases is limited, as its efficacy depends on the ability of the treatment agent to cross the blood-brain barrier. Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). Bevacizumab has been shown to be beneficial to patients who have developed brain metastasis from lung cancer and other solid tumors (17,18). Additionally, bevacizumab therapy has been approved for the treatment of recurrent glioblastoma and is currently being evaluated for the treatment of newly diagnosed glioblastoma, central nervous system lymphoma and secondary cerebral metastases derived from glioblastoma (19). Regarding its mechanism of action, it has been suggested that bevacizumab may not have to cross the blood

brain barrier to function because of its ability to neutralize VEGF in the lumen of the capillaries in the brain (19). In one study, the administration of a bevacizumab-containing chemotherapy regimen following neurosurgery, radiosurgery or WBRT was found to result in an OS of 20.6 months after the diagnosis of brain metastases (20). Another study of 21 cases suggested that bevacizumab plays a role in the treatment of brain metastasis from colorectal cancer; however, no statistically significant result was observed due to the small sample size (21). Chahine *et al* (22) compared two groups of patients with brain metastasis from colorectal cancer. When patients with and without bevacizumab treatment were compared, it was concluded that the antiangiogenic therapy significantly improved median survival. However, the timing of bevacizumab introduction, as well as the clinical response in terms of symptoms and imaging, were not mentioned. In the present case, due to the patient refusing immediate post-radiation infusional therapy, capecitabine was used as an alternative treatment. Capecitabine has been shown to be more beneficial than observation in patients with mCRC (13). However, in the present case, it was not until bevacizumab was administered that the symptoms of the patient fully subsided. These observations suggest that in antiangiogenic-naive patients with little symptomatic improvement following radiation treatment, the addition of bevacizumab to the treatment course later can bring benefits.

In conclusion, the brain is an uncommon site of metastasis in colorectal cancer. Most cases of brain metastasis are asymptomatic. For that reason, the early detection of brain metastasis requires the close monitoring of neurological symptoms. WBRT followed by bevacizumab and chemotherapy show satisfactory results.

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Availability of data and materials

All data generated or analyzed in this study are included in this published article.

Authors' contributions

HVN is the clinical oncologist who treated the patient and revised the manuscript. DTP is the assistant doctor who wrote the manuscript and made substantial contributions to the conception of the study. TTN, KNTM, BTT and HLT assisted in the patient treatment, collected clinical information and assisted with the drafting of the manuscript. HVN and DTP confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for the publication of this study has been obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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