

Neurological Symptom as the First Sign of Colorectal Carcinoma – a Case report

Neurološki simptom kao prvi znak kolorektalnog karcinoma – prikaz slučaja

Ivo Dilber^{1*}, Ivana Radovčić Gauta¹, Lana Jajac Bručić², Iva Škifić³, Željko Čulina⁴, Juraj Prejac⁵

Abstract. Aim: To present a rare case of a patient with an isolated brain metastasis from colorectal carcinoma in whom an extensive diagnostic workup failed to identify the primary tumour. **Case report:** A 73-year-old female patient was admitted to the Neurology Department due to weakness in the right side of her body. Imaging with multislice computed tomography (MSCT) and brain magnetic resonance (MR) confirmed an expansive lesion in the left frontal region with surrounding oedema. Radiological findings suggested either a metastasis or a high-grade primary glioma. As the diagnostic workup did not reveal the primary tumour, the patient was transferred to Clinical Hospital Dubrava for surgical treatment. An intracranial tumour resection was performed with a histopathological confirmation of colon carcinoma metastasis. Postoperative brain irradiation was administered. A positron emission tomography scan (PET) showed focal accumulation of radioisotopes without clear pathological substrate in the appendix and cecoascendent junction area. Repeated colonoscopy did not find any pathological mucosal changes. The patient declined systemic treatment. Overall survival was 11 months, in line with literature data. **Conclusion:** The diagnosis of brain metastases from colorectal carcinoma is very rare, and even rarer is the diagnosis of isolated brain metastases without extracranial progression, counting for <0.5%. Therapeutic options for brain metastases from colorectal carcinoma include surgery, radio-neurosurgery, stereotactic radiotherapy, and brain irradiation. In our opinion, diagnostic evaluation of the central nervous system in patients with colorectal carcinoma should be considered if the patient has neurological symptoms or if there is an increase in carcinoembryonic antigen (CEA) levels without signs of extracranial disease progression.

Keywords: brain; colorectal; neoplasms; neoplasm; metastasis; neurosurgery; radiotherapy

Sažetak. Cilj: Prikazati rijedak slučaj bolesnice s izoliranom presadnicom kolorektalnog karcinoma u mozak kod koje opsežnom dijagnostičkom obradom nije pronađen primarni tumor. **Prikaz slučaja:** Bolesnica u dobi od 73 godine primljena je na Odjel za neurologiju zbog slabosti ekstremiteta desne strane tijela. Učinjene su višeslojna kompjutorizirana tomografija (engl. *multislice computed tomography*; MSCT) i magnetska rezonancija (engl. *magnetic resonance*; MR) mozga kojima je verificiran ekspanzivni proces lijeve frontalne regije s izraženim okolnim edemom. Radiološki nalaz upućivao je na presadnicu ili primarni gliom visokog stupnja. Budući da dijagnostičkom obradom nije pronađen primarni tumor, bolesnica je premještena u Kliničku bolnicu Dubrava radi kirurškog liječenja. Učinjena je operacija intrakranijalnog tumora uz patohistološku potvrdu da se radi o metastazi karcinoma kolona. Nakon operacije provedena je iradijacija mozga. Učinjena je pozitronska emisijska tomografija (engl. *positron emission tomography*; PET) kojom se prikazalo žarišno nakupljanje radiofarmaka (SUVmax = 8,6) bez jasnog patomorfološkog supstrata u području apendiksa i cekoascendentnog prijelaza. Ponovljenom kolonoskopijom nije nađena patološki promijenjena sluznica. Bolesnica je odbila sistemsko liječenje. Sveukupno preživljavanje iznosilo je 11 mjeseci, što je u skladu s podatcima iz literature. **Zaključak:** Dijagnoza moždanih metastaza kolorektalnog karcinoma vrlo je rijetka, dok je još rjeđa dijagnoza izoliranih moždanih metastaza bez ekstrakranijalne progresije te prema literaturi iznosi < 0,5%. U odnosu na liječenje ekstrakranijalnih metastaza kolorektalnog karcinoma, nema konsenzusa u liječenju

¹ Zadar General Hospital, Department of Oncology and Nuclear Medicine, Zadar, Croatia

² General Hospital Šibenik, Department of Internal Medicine, Šibenik, Croatia

³ Clinical Hospital Dubrava, Clinical Institute of Pathology and Citology, Zagreb, Croatia

⁴ Zadar General Hospital, Department of Internal Medicine, Department of Pulmonology, Zadar, Croatia

⁵ University Hospital Center Zagreb, Clinical of Oncology, Zagreb, Croatia

*Corresponding author:

Ivo Dilber, MD

Zadar General Hospital, Department of Oncology and Nuclear Medicine
Boze Pericica 5, 23000 Zadar, Croatia
E-mail: ivodilber81@gmail.com

<http://hrcak.srce.hr/medicina>

moždanih metastaza. Terapijske opcije u liječenju moždanih metastaza kolorektalnog karcinoma uključuju operaciju, radioneurokirurgiju, stereotaksijsku radioterapiju i iradijaciju mozga. Prema našem mišljenju, dijagnostičku obradu središnjeg živčanog sustava kod bolesnika s kolorektalnim karcinomom treba učiniti ako bolesnik ima neurološke simptome ili u slučaju porasta vrijednosti karcinoembrionalnog antigena (engl. *carcinoembryonic antigen*; CEA) bez znakova ekstrakranijalne progresije bolesti.

Ključne riječi: kolorektalni karcinom; mozak; moždane metastaze; neurokirurgija; radioterapija

The location of the primary tumor in the rectum, lung metastases, the presence of a Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation and younger age are considered to be risk factors for brain metastases occurrence.

INTRODUCTION

According to the incidence of malignant diseases in the world, colorectal cancer is in the third place, while in terms of mortality, it is in the second place¹. Currently, at the time of diagnosis of the colorectal cancer, 25% of patients already have distant metastases, while 25% of them get diagnosed with metastatic disease during clinical follow-up after primary tumour surgery². The incidence of brain metastases of colorectal cancer is very low and counts for about 2%²⁻⁸. In relation

to the treatment of extracranial metastases of colorectal cancer, there is no consensus for the treatment of brain metastases⁸. Therapeutic options for the treatment of brain metastases of colorectal cancer include surgery, radio neurosurgery, stereotaxic radiotherapy and whole brain radiotherapy (WBRT)^{2, 9-12}. The best survival was among those patients who underwent multimodal treatment^{2, 9, 10, 13, 14}.

CASE REPORT

A 73-year-old woman was admitted to the Department of Neurology because of weakness in the extremities on the right side of the body. The patient previously had no disturbances with the gastrointestinal system, such as pain, difficulty in bowel movements or blood in the stool. MSCT of the brain was performed in the emergency department, and an MR showing an expansive 25×21×21mm (LL×AP×CC) process of the left frontal region with marked surrounding oedema (Figure 1 a, b). It was highly suspicious of secondaries or a high-grade primary glioma. An additional diagnostic test (MSCT of the thorax, abdomen and pelvis) was performed which verify a non-specific 11 mm nodule in the right lung. Bronchoscopy was negative. Tumour markers (CEA, Ca 19-9, Ca 15-3, Ca 125, Cyfra 21-1) were in the reference values. Complete blood count detected no abnormalities. Oesophagogastrosc-

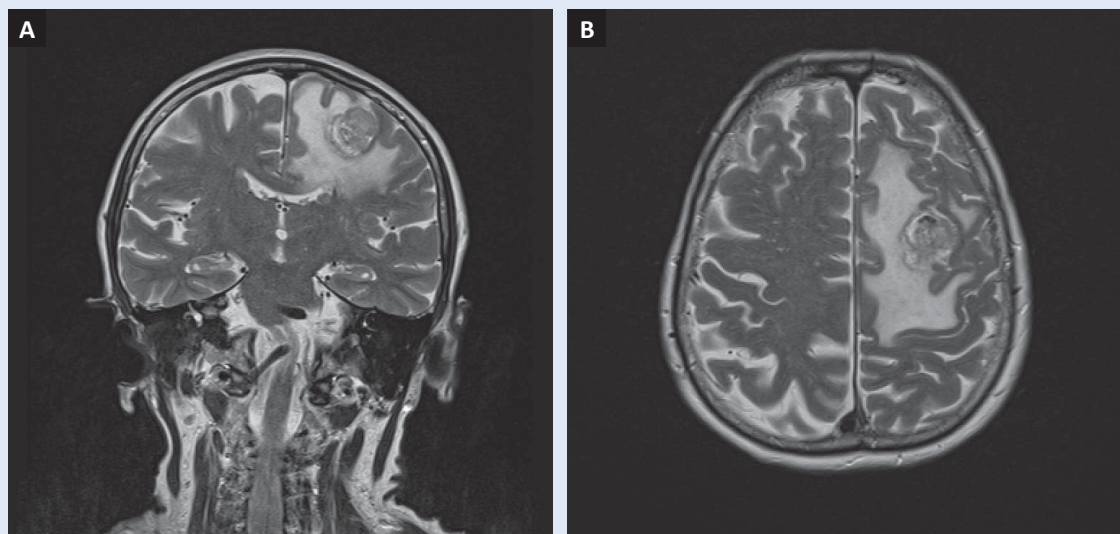


Figure 1. Brain MR – expansive process of frontal left size 25×21×21mm (LL×AP×CC) with marked surrounding edema, (A) coronal view, (B) transverse view.

py and mammography were performed additionally, and results were normal. Colonoscopy was interrupted on two occasions at the patient's request due to pain. After sedation, a total colonoscopy was completed, showing a 10 mm sessile polyp at the 25 cm from anocutaneous border. It was removed with the histopathologic finding corresponding to a tubular adenoma with high degree dysplasia. Considering that no primary tumour was found during the diagnostic workup, the multidisciplinary team decided to operate the lesion in the brain with the aim to histopathological confirm the malignant disease. The patient was transferred to the Clinical Centre for a surgical treatment. Frontal craniotomy and tumour ablation were performed. The histopathological findings corresponded to metastasis of colorectal adenocarcinoma, immunohistochemically thyroid transcription factor (TTF)-1 and cy-

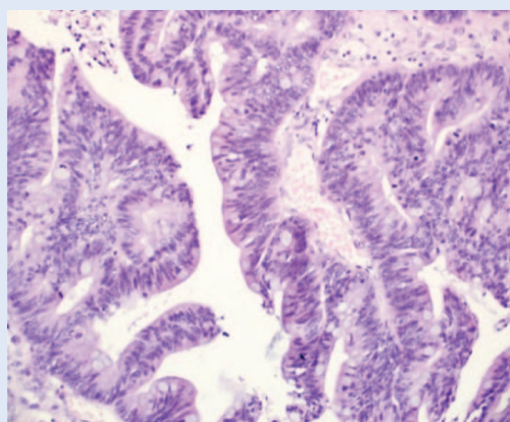


Figure 2. Histopathological analysis of the brain metastasis, HE×20

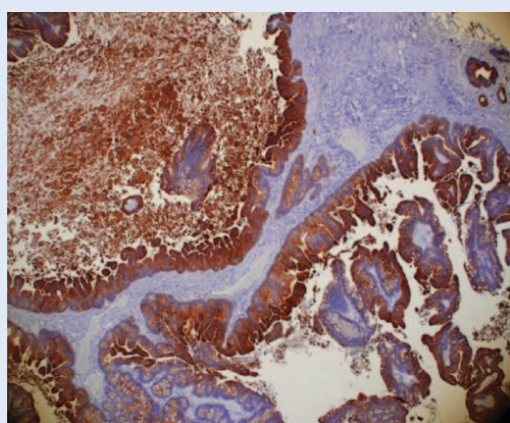


Figure 3. Immunohistochemical analysis of the brain metastasis, CK20 positive result

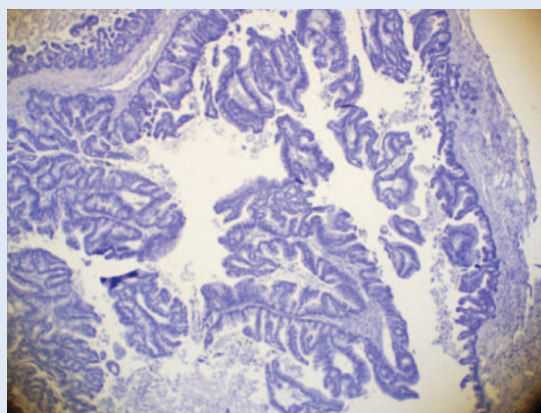


Figure 4. Immunohistochemical analysis of the brain metastasis, CK7 negative result

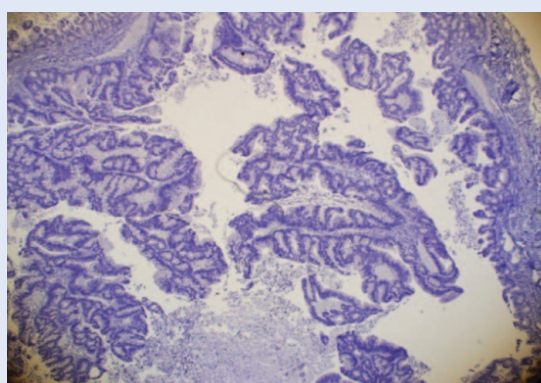


Figure 5. Immunohistochemical analysis of the brain metastasis, TTF1 negative result

tokerin 7 (CK7) were negative, but cytokeratin 20 (CK20), transcription factor CDX-s and special AT-rich sequence-binding protein 2 (SATB2) were positive (Figures 2, 3, 4, 5). Immunohistochemically, it was a microsatellite-stable tumour. A mutation in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene was also detected.

Palliative brain irradiation (WBRT, TD 30Gy/10×) was performed. PET scan discovered a more focal accumulation of radiopharmaceuticals (SUVmax 8.6) without a clear pathomorphological substrate in the area of cecoascending transition and the appendix (Figure 6). Minimal metabolic activity (SUVmax 1.5) of the right lung nodule was detected. After inspection of the PET scan findings, the colonoscopy was repeated, but no pathologically altered mucous membrane was found. In agreement with patient's family, she decided not to pursue active systemic oncologic treatment.

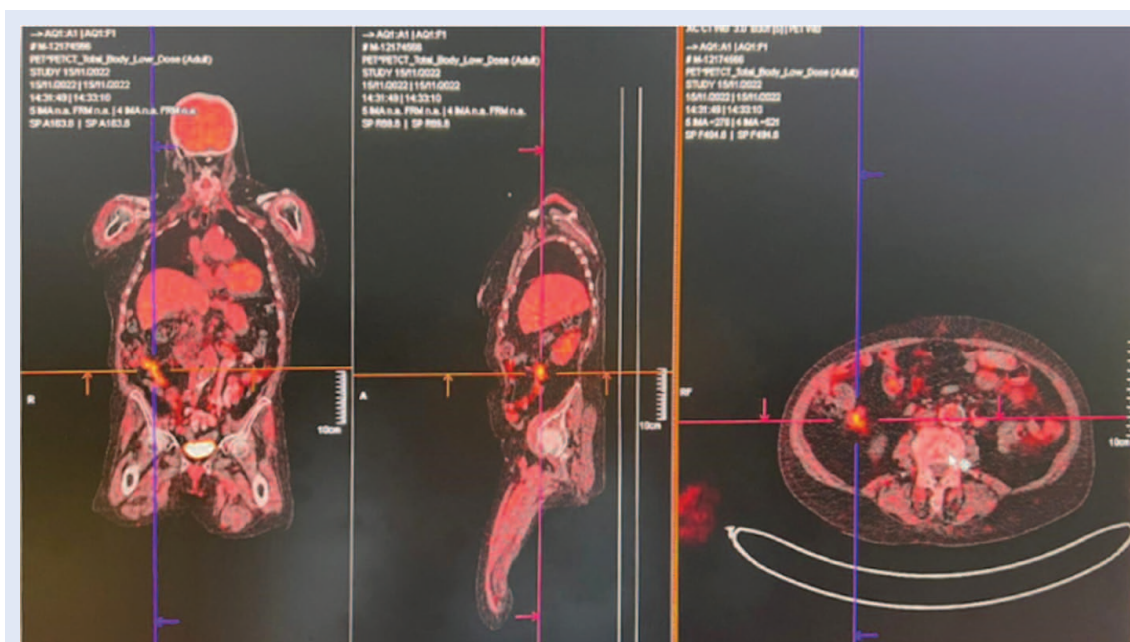


Figure 6. PET scan – focal accumulation of radiopharmaceuticals (FDG) in the area of cecoascending transition and the appendix

DISCUSSION

In 2020, 1.9 million patients with colorectal cancer were diagnosed in the world, of which 0.9 million died of this diagnosis^{1,15}. At the time of the diagnosis of colorectal cancer, 25% of patients have distant metastases, while 25% of them get diagnosed with metastatic disease during clinical follow-up after primary tumour surgery². The diagnosis of brain metastases is 3-10 times more frequent than the diagnosis of a primary central nervous system (CNS) tumour^{4,16}. According to the frequency in adult, lung cancer metastasizes to the brain most often (36-64%), followed by breast cancer (15-25%) and melanoma (5-20%)³. The occurrence of brain metastases from colorectal cancer is very low²⁻⁸. According to research by S. Muller and associates, it is only 2.1% (in the range from 0.1% to 11.5%)². Incidence of isolated metastases of colorectal cancer to the brain without extracranial progression is even rarer, <0.5%⁷⁻⁹. In their work, Christiansena and colleagues report a slightly higher frequency of brain metastases in Americans (1.82%) and Europeans (1.55%) compared to the Asian population (1.21%)³. Approximately 90% of patients with newly discovered brain metastases from

colorectal cancer also have metastases in other organs, most often in the lungs (71-92%) and liver (36.6-68%)^{7,13}. The majority of patients diagnosed with brain metastases from colorectal cancer were asymptomatic^{2,13}. National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines do not advise routine radiological imaging of the CNS among patients who do not have neurologic symptoms and are being treated for colorectal cancer^{2,10}. Symptomatic disease is most often presented in the form of an epileptic attack, signs of increased intracranial pressure or other neurological symptoms². Rectal cancer, lung metastases, mutation in the KRAS gene, elevated CEA values and younger age are listed as risk factors for the occurrence of brain metastases from colorectal cancer^{2,3,10,13,19}. Of the risk factors, our patient only had mutation in the KRAS gene. The first-line treatment of metastatic, microsatellite-stable, colorectal cancer includes chemotherapy based on oxaliplatin or irinotecan with the addition of targeted therapy (Monoclonal Anti Vascular Endothelial Growth Factor Receptor 2 Antibody, Anti-Epidermal Growth Factor Receptor), depending on the localization of the primary tumour, the findings of molecular testing (RAS

proteins, BRAF gene, Human Epidermal Growth Factor Receptor 2), the treatment goal and patients requests^{16–18}. In relation to the treatment of extracranial metastases of colorectal carcinoma, there is no consensus regarding the treatment of brain metastases^{8,20}. Therapeutic options for colorectal cancer brain metastases include surgery, radio neurosurgery, stereotaxic radiotherapy and WBRT^{2,9–12}. Patients who underwent multimodal treatment had the best survival rate^{2,9,10,13,14,23}. In their work, Zhaohui et al retrospectively analysed 104 patients with brain metastases from colorectal cancer⁷. According to research data, patients who received more aggressive, multimodal treatment had the best survival⁷. The median overall survival in patients who did not receive any treatment was 0.43 months. The median overall survival in patients who underwent only WBRT was 3.13 months and those patients who underwent operative treatment had a median overall survival of 4.8 months. Patients who underwent WBRT with systemic chemotherapy had a median overall survival of 12.2 months. In those who underwent surgery with postoperative radiation, the median overall survival was 14 months. The longest median overall survival (41.1 months) was in patients who underwent surgery following radiation and systemic chemotherapy⁷. As in our case, solitary brain metastasis detected prior to primary colorectal cancer diagnosis is very rare.

Although total colonoscopy is considered reliable in detecting colorectal cancer, in our patient, despite the histopathological and PET scan findings, repeated colonoscopies failed to prove a primary tumour. According to Bressler et al., 4% of patients who were operated for cancer of the right colon in their personal anamnesis had a normal colonoscopy finding 6–36 months before the operation of the primary tumor²¹. According to Hooi C Ee and colleagues, in a 5–year follow-up among people who had a proper initial colonoscopy, colorectal cancer was detected in only 0.5% of examinations²².

We decided to present this patient because it is a rare case of isolated brain metastasis of colorectal cancer as the first sign of a malignant disease. We failed to prove the primary tumour by means

of extensive diagnostic workup, but the histopathological diagnosis was established after brain metastasis surgery. The patient underwent palliative brain irradiation after the operation. Systemic treatment with chemotherapy was planned, but the patient refused further active oncological treatment.

Diagnostic work-up of the central nervous system (CNS) should be done if patient has neurological symptoms, or in case of increase in carcinoembryonic antigen (CEA) without signs of extracranial disease.

CONCLUSION

Brain metastases of colorectal cancer are rare, but isolated brain metastases without extracranial progression are even rarer. The location of the primary tumour in the rectum, lung metastases, the presence of a KRAS mutation and younger age are considered risk factor for their occurrence. In our opinion diagnostic work-up of the CNS should be done if patient has neurological symptoms, or in case of increase in CEA without signs of extracranial disease. Given that there are no clear guidelines for the treatment of brain metastases from colorectal cancer, the choice of treatment modality should be made individually for each patient, relying on risk factors and the patient's desires. If patient's general condition is good, multimodal treatment (surgery, stereotaxic radiotherapy ± WBRT and chemotherapy) obtains the best results in terms of delayed disease progression and overall survival. The first sign of colorectal cancer for our patient was weakness in the extremities on the right side of the body. No primary tumour was found after extensive diagnostic workup. The histopathological pattern of the primary lesion of the brain undoubtedly indicated that it was a metastasis of colorectal cancer. The patient underwent palliative brain irradiation after the operation but refused further systemic treatment. The overall survival was 11 months which corresponds to data found in the literature.

Conflicts of Interest: Authors declare no conflicts of interest.

REFERENCES

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol* 2021;14:101174.
2. Müller S, Köhler F, Hendricks A, Kastner C, Börner K, Diers J et al. Brain Metastases from Colorectal Cancer: A Systematic Review of the Literature and Meta-Analysis to Establish a Guideline for Daily Treatment. *Cancers (Basel)* 2021;13:900.
3. Christensen TD, Spindler KL, Palshof JA, Nielsen DL. Systematic review: brain metastases from colorectal cancer—Incidence and patient characteristics. *BMC Cancer* 2016; 16:260.
4. Franchino F, Rudà R, Soffiotti R. Mechanisms and Therapy for Cancer Metastasis to the Brain. *Front Oncol* 2018;8: 161.
5. Finkelmeier F, You SJ, Waidmann O, Wolff R, Zeuzem S, Bähr O et al. Bevacizumab in Combination with Chemotherapy for Colorectal Brain Metastasis. *J Gastrointest Cancer* 2016;47:82-8.
6. Roussille P, Auvray M, Vansteene D, Lecomte T, Rigault E, Maillet M et al. Prognostic factors of colorectal cancer patients with brain metastases. *Radiother Oncol* 2021; 158:67-73.
7. Mjahed RB, Astaras C, Roth A, Koessler T. Where Are We Now and Where Might We Be Headed in Understanding and Managing Brain Metastases in Colorectal Cancer Patients? *Curr Treat Options Oncol* 2022;23:980-1000.
8. Esplin BL, Hubbard J. Isolated Cerebellar Metastasis as the Initial Manifestation of Right-Sided Colon Cancer: A Case Report and Review of Current Management Strategies. *Colorectal cancers* 2016;2:1-4.
9. Tagayasu Y, Miyamoto Y, Sawayama H, Ogawa K, Kato R, Yoshida N et al. Rectal cancer diagnosed after resection of isolated brain metastasis. *Surg Case Rep* 2022;8:52.
10. Wang D, Chen C, Ge X, Yang Q, Huang Y, Ling T et al. Factors Prognostic for Brain Metastases from Colorectal Cancer: A Single-Center Experience in China. *Cancer Manag Res* 2021;13:6767-6774.
11. McKay MJ. Brain metastases: increasingly precision medicine—a narrative review. *Ann Transl Med* 2021;9: 1629.
12. Chu C, Navalkissoor S, Gillmore R. Neurological symptoms from a brain metastasis as the first presentation of colorectal cancer. *BMJ Case Rep* 2015;2015:2015210422.
13. Majd N, Simon M, Wagman R, Gesner L. A Rare Case of Colon Cancer Metastasis to the Brain and a Brief Review of its Treatment and Prognosis. *Radiol Case Rep* 2021;17:696-699.
14. Rades D, Raabe A, Bajrovic A, Alberti W. Treatment of solitary brain metastasis. Resection followed by whole brain radiation therapy (WBRT) and a radiation boost to the metastatic site. *Strahlenther Onkol* 2004;180:144-7.
15. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M et al. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut* 2023;72:338-344.
16. Mjahed RB, Astaras C, Roth A, Koessler T. Where Are We Now and Where Might We Be Headed in Understanding and Managing Brain Metastases in Colorectal Cancer Patients? *Curr Treat Options Oncol* 2022;23:980-1000.
17. National Comprehensive Cancer Network [Internet]. Plymouth Meeting: NCCN Guidelines Version 2.2023 Colon Cancer, c2024 [cited 2023 May 25]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
18. Yoshino T, Cervantes A, Bando H, Martinelli E, Oki E, Xu RH et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with metastatic colorectal cancer. *ESMO Open* 2023;8:101558.
19. Shaikh AS, Pavurala R, Gou E. Brain Metastasis in a Young Patient: Consider the Rectum. *Cureus* 2021;13:20055.
20. Cherfane C, Kapadia MR, Schey R, Holm A. Curative Intent Treatment for Colorectal Cancer with Isolated Brain Metastases: A Case Report. *J Carcinog* 2014;10:002.
21. Bressler B, Paszat LF, Vinden C, Li C, He J, Rabeneck L. Colonoscopic miss rates for right-sided colon cancer: a population-based analysis. *Gastroenterology* 2004;127:452-6.
22. Ee HC, Semmens JB, Hoffman NE, Perth Teaching Hospitals Endoscopy Group. Complete colonoscopy rarely misses cancer. *Gastrointest Endosc* 2002;55:167-71.
23. Mege D, Ouaiissi M, Fuks D, Metellus P, Peltier J, Dufour H et al. Patients with brain metastases from colorectal cancer are not condemned, *Anticancer Res* 2013;33:5645-5648.