DOI: https://doi.org/10.2298/SARH200322025S
UDC: 616.351-006.6-08

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Can multidisciplinary approach win the battle against metastatic rectal cancer?

Suzana Stojanović-Rundić[1,2], Vesna Plešinac-Karapandžić[1,2], Jelena Dedović-Stojaković[1], Nenad Mijalković[3], Violeta Škrelja[3], Nebojša Miletić[1], Aleksandra Đurić-Stefanović[2,4]

[1]Institute for Oncology and Radiology of Serbia, Department of Radiation Oncology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Clinic for Gastroenterology and Hepatology, Department of Digestive Oncology, Belgrade, Serbia;
[4]University Clinical Center of Serbia, Unit of Digestive Radiology, Center of Radiology and MR, Belgrade, Serbia

SUMMARY

Introduction Colorectal cancer is the third most common cancer and one of the leading causes of cancer-related deaths in men and women worldwide. The contemporary multidisciplinary approach has decreased rates of local recurrence and improved outcomes in metastatic colorectal cancer. We present a case of a primarily metastatic rectal cancer patient who underwent multidisciplinary planned treatment and showed complete response with now three years disease-free survival.

Case outline A 61-year-old female was diagnosed with a T4N2M1a rectal adenocarcinoma at the age of 58. She underwent six cycles of systemic chemotherapy capecitabine-oxaliplatin plus bevacizumab with partial response confirmed by diagnostic imaging procedures. According to multidisciplinary board decision, preoperative radiotherapy treatment was administered with concomitant capecitabine-based chemotherapy. A 50.4 Gy total dose was delivered with 1.8 Gy fraction dose. After concomitant chemoradiotherapy treatment, two more cycles of systemic chemotherapy capecitabine-oxaliplatin plus bevacizumab were administered. One month after completion of systemic chemotherapy, primary rectal cancer was operated with a complete response on histopathologic specimens. Six weeks following previous surgery, metastasectomy of lung deposits was performed; histopathology confirmed metastatic adenocarcinoma of colorectal origin. Three more cycles of postoperative chemotherapy capecitabine-oxaliplatin plus bevacizumab were administered.

Conclusion On regular follow-up, no evidence of disease was shown, with disease-free survival of three years. The treatment improved the patient's quality of life.

Keywords: chemotherapy; radiotherapy; rectal cancer; stage IV; surgical treatment

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and one of the leading causes of cancer-related deaths in men and women worldwide [1]. Approximately 30% of CRC refers to rectal cancer (RC), which is associated with poorer clinical outcomes. Metastases will occur in 20–50% of patients with RC [2, 3]. Contemporary multidisciplinary planned treatment has decreased rates of local recurrence in RC and improved outcomes in metastatic CRC (mCRC) [4]. It is important to evaluate characteristics of patients and of the disease, such as the extent of primary and metastatic disease, in order to select and deliver the appropriate treatment. The goal is personalized medicine, to individualize the treatment according to the patient and the disease [5].

We report a case of a primarily metastatic RC patient who underwent multidisciplinary planned treatment and showed a complete response with now three years disease-free survival.

CASE REPORT

The patient was diagnosed with stage IVa RC at the age of 58. She had been suffering from symptoms of hemorrhoid disease for several years. In December 2016, shortly after the onset of new symptoms indicative for CRC, such as rectorrhagia, changes in bowel habits, frequent tenesmus, the patient was diagnosed with metastatic RC. The patient's baseline Eastern Cooperative Oncology Group performance status (ECOG PS) was 1. Digital rectal examination revealed tumor mass related to RC. Serum levels of tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9) were within normal ranges. Colonoscopy performed in January 2017 showed a tumor mass in the rectum with the distal end located 7 cm from the anal verge. Histopathology (HP) examination revealed an exulcerated invasive rectal adenocarcinoma, G1. Magnetic resonance imaging (MRI) of the abdomen and the pelvis (Figure 1a) performed in January 2017 showed a 7-cm-long tumor mass in the rectum located within 8 cm of the anal verge, which occupied entire colon lumen in its caudal part, and predominantly

Received • Примљено: March 22, 2020
Revised • Ревизија: March 4, 2021
Accepted • Прихваћено: March 30, 2021
Online first: April 1, 2021

Correspondence to:
Jelena DEDOVIĆ-STOJAKOVIĆ
Department of Radiation Oncology
Institute for Oncology and Radiology of Serbia
Pasterova 14
11000 Belgrade, Serbia
jdedovicstojakovic@gmail.com

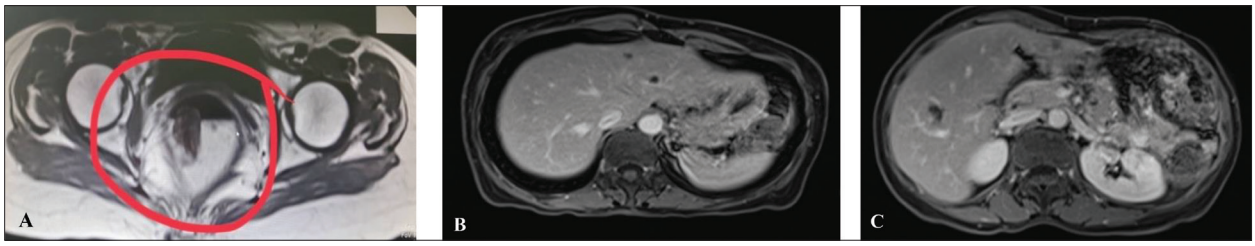

Figure 1. Initial magnetic resonance imaging of the abdomen and the pelvis in the axial plane: (A) on post-contrast T1w sequence, a tumor mass located in the rectum, penetrating all layers of the poster wall and infiltrating perirectal fat up to 30 mm, expanding to the mesorectal fascia bilaterally (mrT3d stage, MF+); (B) and (C) on post-contrast T1FSw sequence, cysts and hemangiomas in the liver (no metastatic lesions)

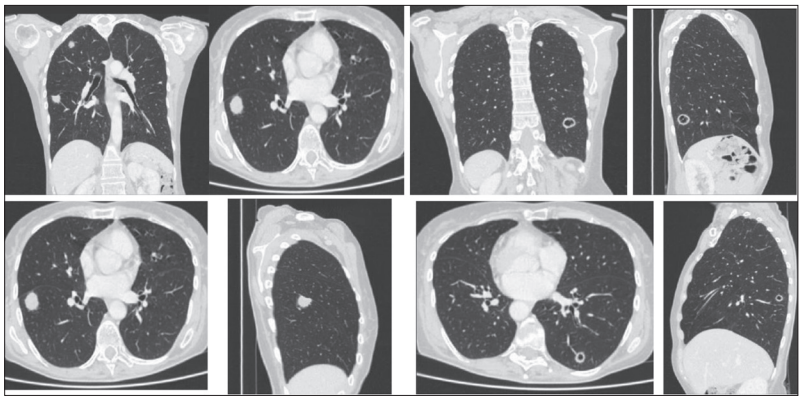

Figure 2. Initial contrast-enhanced chest computed tomography in the axial, coronal, and sagittal planes showing multiple nodular and excavated nodular lesions in both lungs: in the apical segment of the upper right lobe 12 mm, in the apicoposterior segment of the upper left lobe 11 mm, in the anterior segment of the upper left lobe 10 mm, in the superior segment of the upper right lobe 20 mm; bilaterally in basal segments one change on each side of the lung was described, measuring 12 mm in the right lung and 20 mm in the left lung

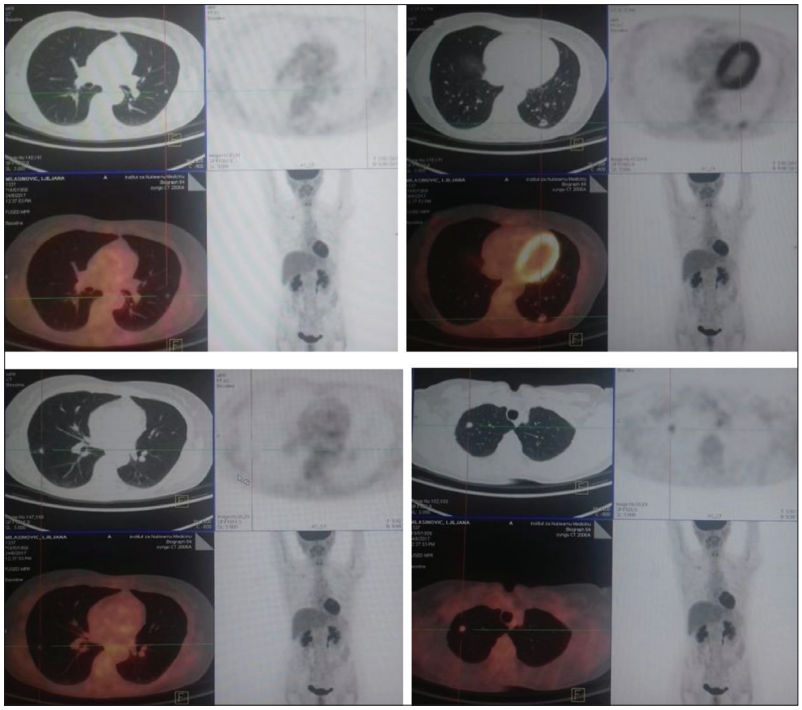

Figure 3. 18F-FDG positron emission computed tomography scans in the axial and coronal planes after systemic chemotherapy, demonstrating four nodular lung lesions with an increased uptake of the radiopharmaceutical

both lateral and posterior colon walls in its cranial part. The tumor penetrated all layers of the posterior and both lateral colon walls and infiltrated perirectal fat up to 30 mm, expanded to the mesorectal fascia bilaterally, reaching approximately 10 mm from the sacral bone. Lymph nodes in perirectal fat were enlarged, measuring 8 mm in diameter. The initial stage estimated according to the MRI was T3d, N2, circumferential resection margin +. In liver, two hemangiomas were shown in the third and the sixth segment, as well as four cysts in the second and the seventh segment (Figure 1b-c).

Chest computed tomography (CT) performed in January 2017 showed six nodular lung lesions, measuring ≤ 20 mm in the greatest diameter (Figure 2).

The pretreatment stage was determined as T4N2M1a (IVa) according to the American Joint Committee of cancer, seventh edition. According to the protocol, the treatment started with six cycles of systemic chemotherapy (CTx) including capecitabine-oxaliplatin (CAPOX) plus bevacizumab. Oxaliplatin (100 mg/m^2) and bevacizumab (400 mg) were administered as intravenous infusion on day 1 every three weeks. Capecitabine was given orally in an appropriate dose divided into two split doses for 14 days, followed by seven days' rest, repeated every three weeks. In May 2017, after completion of six cycles of systemic CTx, partial response of primary RC and lung deposits was confirmed in accordance with Response Evaluation Criteria in Solid Tumors guidelines. MRI of the abdomen and the pelvis showed a post-therapy altered tumor mass located within 8 cm of the anal verge, involving entire circumference and penetrating all layers of the colon, with its thickening up to 10 mm (previously it was 30 mm, then 14 mm). Chest CT was described as in regression with an unchanged number of lung lesions.

According to a multidisciplinary board decision, preoperative three-dimensional conformal radiotherapy (RT) treatment (6-MV photon posterior direct field, 15-MV photon opposed two lateral fields) was administered with

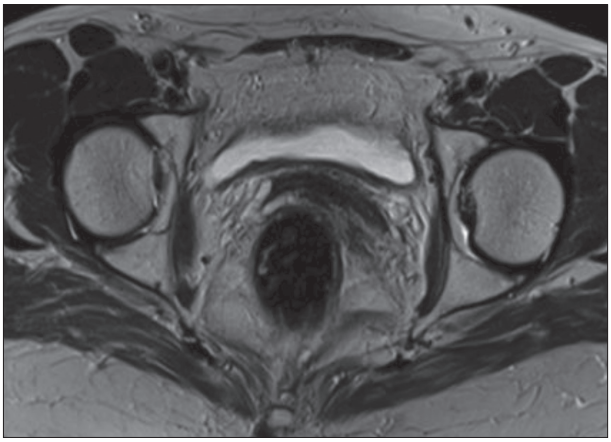

Figure 4. Magnetic resonance image of the pelvis after chemoradiotherapy of rectal cancer, in axial T2w sequence demonstrating complete regression of the rectal tumor

concomitant CTx. A 50.4 Gy total dose with 1.8 Gy in 28 fractions was given five times a week. Concomitant capecitabine-based CTx (825 mg/m^2) was administered twice daily, five days a week during RT. Treatment-related toxicity during chemoradiotherapy (CRT) included diarrheas and tenesmus. In July 2017, after CRT completion, two more cycles of systemic CTx CAPOX plus bevacizumab were administrated. Because of adverse events during CTx, such as sensory neuropathy, hand-foot syndrome, and neutropenia, doses of oxaliplatin and capecitabine were reduced.

In August 2017, fluoro-2-deoxy-D-glucose positron emission CT (^{18}F-FDG PET-CT) showed four lung lesions with an increased uptake of the radiopharmaceutical, while uptake of the pharmaceutical in the rectum was not detected (Figure 3). Complete regression of the primary tumor was described. Chest and abdomen CT from August 2017 showed stable disease. Pelvis MRI was also performed in August 2017 and revealed complete regression of the rectal tumor (Figure 4).

One month after systemic CTx completion, our patient underwent surgical treatment – low anterior resection of the rectum with coloanal anastomosis was performed; HP results showed no evidence of malignancy. Six weeks following previous surgery, metastasectomy of the lung deposits was performed; HP results confirmed metastatic adenocarcinoma of colorectal origin. From January to March 2018, three more cycles of postoperative CTx CAPOX plus bevacizumab were administrated with a total of 11 cycles of CTx. Treatment-related toxicity included oxaliplatin-induced allergic reaction, due to which premedication was prescribed. In March 2018, chest-abdomen-pelvis CT showed no signs of local recurrence (Figure 5).

Chest-abdomen-pelvis CT scans performed in March 2019 showed no evidence of disease. Further follow-up included serum tumor markers, which were within normal ranges, and ^{18}F-FDG PET-CT showed no signs of local recurrence, nor pathological lymph nodes. The patient is ECOG PS zero with a disease-free survival period of three years. The treatment has improved the patient's quality of life.

Informed consent was obtained from the patient for publication of this report and any accompanying images.

DISCUSSION

Previous studies reported that 20% of patients with CRC have distant metastasis at presentation and that 20–50% of patients with RC developed metastatic disease, mostly in the liver, lung, peritoneum, bone and extra-regional lymph nodes [2, 6–9]. These patients have a five-year survival of 13.1% compared to 90.1% for non-metastatic patients [9]. Due to the progress in personalized medicine, significant development has been reached in the treatment of patients with mCRC, which has encouraged a more developed collaboration between multidisciplinary teams and led to progress in survival rate and median survival duration [10, 11, 12]. According to the European Society for Medical Oncology consensus guidelines, a patient with mCRC may reach an overall survival of 30 months as a result of a treatment decision reached multidisciplinary [11, 13]. Nevertheless, the median overall survival in patients with mCRC has increased and it has been reaching over 40 months in molecularly selected patients [4]. A previously published randomized phase III study that evaluated the use of bevacizumab in combination with oxaliplatin-based CTx as the first-line therapy in mCRC, had shown

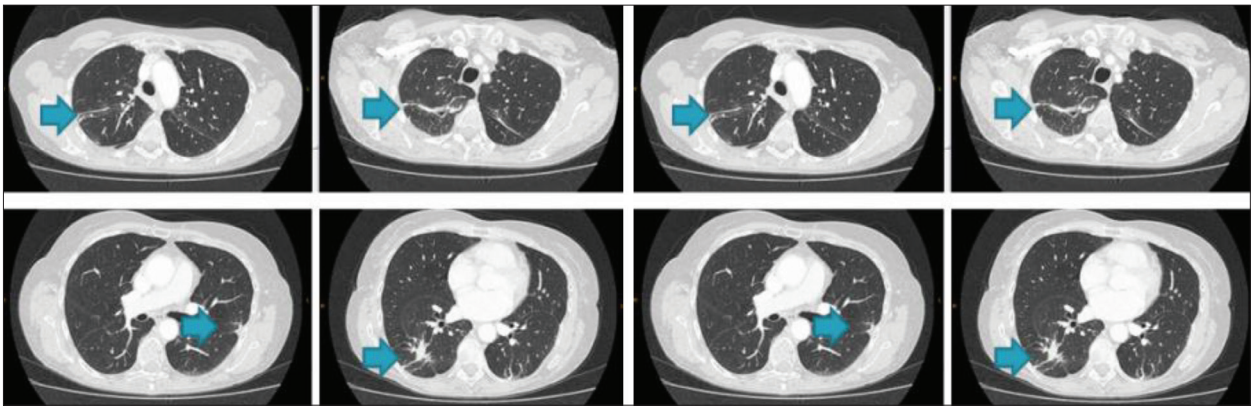

Figure 5. Chest computed tomography in axial planes after lung metastasectomy demonstrating no signs of metastatic recurrence; only fibrotic changes are visible

that the use of bevacizumab to oxaliplatin CTx improved progression-free survival, whereas overall survival differences and response rate were not improved by the addition of bevacizumab [14].

There are still some issues in the treatment of mCRC that need to be clarified, such as the best treatment modality, which regimens to administer in different patients and situations, when to start and when to finish treatment if a response is seen. According to Foubert et al. [15], patients with mCRC can be candidates for multiple lines of therapy. The decision should be based on characteristics of the patient and cancer including tumor biology, and it also depends on previously used therapies. In patients with unresectable mCRCs, multiple lines of therapy should be assessed. The never-used agent should be considered if the patient has not already been treated with all major CTx agents; also, a drug previously used with a good response could be reintroduced. Various options can be discussed, patients should be considered for inclusion in clinical trials [15].

A study by van Dijk et al. [16], which included 50 adult patients with primary metastasized RC, has shown that radical surgical treatment of all tumor sites conducted after short-course RT and bevacizumab plus CAPOX combination therapy may potentially enable the treatment of metastatic disease and good control of the primary RC.

For patients with metastatic RC and resectable primary tumor, as well as lung or liver metastases, the resection of both tumor sites is recommended [17]. Surgical treatment for liver and pulmonary metastases in selected mCRC patients may improve survival and prognosis. The five-year survival for mCRC patients with liver metastases who underwent surgical treatment reaches 58%, whereas the survival rate for mCRC patients with liver metastasis without surgical treatment ranges 20–24 months [18, 19]. Pulmonary resection for metastases from CRC may improve survival in selected patients. Thus, the outcome may vary due to the timing of surgical treatment [20]. Yamada et al. [21] showed that a follow-up of nine months from the date of pulmonary metastasis diagnosis to metastasectomy is associated with improved prognosis [21].

In our patient, the collaboration of multidisciplinary cancer management team supported by evidence-based guidelines made it possible to achieve better local control and longer survival followed by improved quality of life. With advances in cancer treatment modalities, comprising surgery, radiotherapy, and systemic treatment, we hope that the number of cancer survivors with metastatic disease will be significantly increased.

Conflict of interest: None declared.

REFERENCES

1. Favoriti P, Carbone G, Greco M, Pirozzi F, Pirozzi RE, Corcione F. Worldwide burden of colorectal cancer: a review. Updates Surg. 2016;68(1):7–11.
2. Al Hillan A, Al-Banaa K, Mohamed M, Hawa F, Turtel P. A Case of Late Recurrence of Colon Cancer After Curative Treatment. Cureus. 2020;12(5):e8083.
3. Bozkaya Y, Albayrak I, Tucer D, Kaya Z, Usta U. Late-Onset Lung Metastasis in Rectum Cancer Can Be Confused with Primary Lung Cancer; a Case Report and Literature Review. J Gastrointest Cancer. 2019;50(4):1029–33.
4. Salvatore L, Aprile G, Arnoldi E, Aschele C, Carnaghi C, Cosimelli M, et al. Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM). ESMO Open. 2017;2(1):e000147.
5. Noh GT, Han J, Cho MS, Hur H, Lee KY, Kim NK, et al. The impact of early adjuvant chemotherapy in rectal cancer. PLoS One. 2020;15(1):e0228060.
6. Biller LH, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. JAMA. 2021;325(7):669–85.
7. Vera R, Gómez ML, Ayuso JR, Figueras J, García-Alfonso P, Martínez V, et al. Correlation of RECIST, Computed Tomography Morphological Response, and Pathological Regression in Hepatic Metastasis Secondary to Colorectal Cancer: The AVAMET Study. Cancers (Basel). 2020;12(8):2259.
8. Pan HD, Zhao G, An Q, Xiao G. Pulmonary metastasis in rectal cancer: a retrospective study of clinicopathological characteristics of 404 patients in Chinese cohort. BMJ Open. 2018;8(2):e019614.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
10. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75.
11. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422.
12. You XH, Jiang YH, Fang Z, Sun F, Li Y, Wang W, et al. Chemotherapy plus bevacizumab as an optimal first-line therapeutic treatment for patients with right-sided metastatic colon cancer: a meta-analysis of first-line clinical trials. ESMO Open. 2020;4(Suppl 2):e000605.
13. Rumpold H, Niedersüß-Beke D, Heiler C, Falch D, Wundsam HV, Metz-Gercek S, et al. Prediction of mortality in metastatic colorectal cancer in a real-life population: a multicenter explorative analysis. BMC Cancer. 2020;20(1):1149.
14. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26(12):2013–9.
15. Foubert F, Matysiak-Budnik T, Touchefeu Y. Options for metastatic colorectal cancer beyond the second line of treatment. Dig Liver Dis. 2014;46(2):105–12.
16. van Dijk TH, Tamas K, Beukema JC, Beets GL, Gelderblom AJ, de Jong KP, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol. 2013;24(7):1762–9.
17. Tong D, Liu F, Li W, Zhang W. The impacts of surgery of the primary cancer and radiotherapy on the survival of patients with metastatic rectal cancer. Oncotarget. 2017;8(51):89214–27.
18. Jeong S, Heo JS, Park JY, Choi DW, Choi SH. Surgical resection of synchronous and metachronous lung and liver metastases of colorectal cancers. Ann Surg Treat Res. 2017;92(2):82–9.
19. Montalvo-Javé EE, Jiménez Bobadilla B, Espejel Deloiza M, Aguilar Preciado IH, Negrete Cervantes LF, Diliz-Pérez H. Synchronous Resection of Colon Adenocarcinoma and Bisegmentectomy of Liver Metastases. Case Rep Gastroenterol. 2019;13(2):238–44.
20. Okumura T, Boku N, Hishida T, Ohde Y, Sakao Y, Yoshiya K, et al. Surgical Outcome and Prognostic Stratification for Pulmonary Metastasis from Colorectal Cancer. Ann Thorac Surg. 2017;104(3):979–87.
21. Yamada K, Ozawa D, Onozato R, Suzuki M, Fujita A, Ojima H. Optimal timing for the resection of pulmonary metastases in patients with colorectal cancer. Medicine (Baltimore). 2020;99(9):e19144.

Да ли се мултидисциплинарним приступом у лечењу може победити метастатски карцином ректума?

Сузана Стојановић-Рундић[1,2], Весна Плешинац-Карапанџић[1,2], Јелена Дедовић-Стојаковић[1], Ненад Мијалковић[3], Виолета Шкреља[3], Небојша Милетић[1], Александра Ђурић-Стефановић[2,4]

[1]Институт за онкологију и радиологију Србије, Клиника за радиолошку онкологију и дијагностику, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за гастроентерологију и хепатологију, Одељење за дигестивну онкологију, Београд, Србија;
[4]Универзитетски клинички центар Србије, Одељење за дигестивну радиологију, Центар за радиологију и МР, Београд, Србија

САЖЕТАК

Увод Колоректални карцином је трећи најчешћи карцином и један је од водећих узрока смрти повезаних са карциномима код жена и мушкараца широм света. Савременим, мултидисциплинарним приступом у лечењу смањена је учесталост појаве локалног рецидива и побољшани су исходи лечења код метастатског колоректалног карцинома. Приказали смо болесницу са примарно метастатским карциномом ректума која је лечена мултидисцилинарним приступом и код које је испољен комплетни одговор са периодом преживљавања без прогресије болести од три године.

Приказ болесника Код шездесетједногодишње болеснице постављена је дијагноза аденокарцинома ректума стажираног као *T4N2M1a* у 58. години живота. Болесница је примила шест циклуса системске хемотерапије капецитабином/оксалиплатином уз бевацизумаб, дијагностичким имиџинг процедурама процењена је парцијална регресија. Сходно одлуци мултидисциплинарног тима, ординирана је преоперативна радиотерапија уз конкомитантну хемотерапију капецитабином. Примењена је укупна доза од 50,4 *Gy* са појединачном дозом по фракцији од 1,8 *Gy*. После завршетка конкомитантне хеморадиотерапије ординирана су још два циклуса системске хемотерапије капецитабином/оксалиплатином уз бевацизумаб. Месец дана после завршетка примене системске хемотерапије оперисан је примарни тумор ректума са верификованом комплетном регресијом у хистопатолошком налазу. Шест недеља после претходно наведене операције учињена је метастазектомија депозита у плућима; хистопатолошки је потврђено присуство метастатског аденокарцинома колоректалног порекла. Ординирана су још три циклуса постоперативне хемотерапије капецитабином/оксалиплатином уз бевацизумаб.

Закључак При редовним контролним прегледима није доказано присуство болести, при чему је период преживљавања без прогресије болести три године. Лечење је поправило квалитет живота болеснице.

Кључне речи: карцином ректума; радиотерапија; хемотерапија; хируршко лечење; IV стадијум