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Paper Accepted*

ISSN Online 2406-0895

Case Report / Приказ болесника

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Can multidisciplinary approach win the battle against metastatic rectal cancer?

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

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Received: March 22, 2020
Revised: March 4, 2021
Accepted: March 30, 2021
Online First: April 1, 2021
DOI: https://doi.org/10.2298/SARH200322025S

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
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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

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 метастатког колоректалног карцинома. Приказали смо пацијенткињу са примарно метастатским карциномом ректума која је лечена мултудисцилинарним 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 капецитабин-оксалиплатин 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 капецитабин-оксалиплатин уз бевацизумаб. Месец дана после завршетка примене системске хемотерапије, учињена је операција примарног тумора ректума са верификованом комплетном регресијом у хистопатолошком налазу. Шест недеља после претходно наведене операције учињена је метастазектомија депозита у плућима; хистопатолошки потврђено је присуство метастатског аденокарцинома колоректалног порекла. Ординирана су још три циклуса постоперативне хемотерапије капецитабин-оксалиплатин 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

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 worse clinical outcomes. In 20% – 50% of patients with RC metastases will occur [2, 3]. Contemporary multidisciplinary decision 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, 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 decision planned treatment and showed a complete response with now three years disease-free survival (DFS).

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 onset of new symptoms indicative for CRC such as rectorrhagia, changes in bowel habits, frequent tenesmus, patient was diagnosed with metastatic RC. The patient's baseline Eastern Cooperative Oncology Group performance status (ECOG PS) was one. 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 tumor mass in 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 abdomen and pelvis (Figure 1 a) performed in January 2017 showed 7-cm-long tumor mass in rectum located within 8 cm of the anal verge, which occupied entire colon lumen in its' caudal part, and predominantly both lateral and posterior colon walls in its' cranial part. 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 sacral bone. Lymph nodes in perirectal fat were enlarged, measuring 8 mm in diametar. The initial stage estimated according to the MRI was T3d, N2, circumferential resection margine +. In liver, two hemangiomas were shown in 3rd and in 6th segment, as well as four cysts in 2nd and in 7th segment (Figure 1 b-c).

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

The pretreatment stage was determined as T4N2M1a (IVa) according to the American Joint Committee of cancer, 7th ed. According to the protocol, the treatment started with six cycles of systemic chemotherapy (CT) including Capecitabine-Oxaliplatin (CAPOX) plus Bevacizumab. Oxaliplatin (100 mg/m^2) and Bevacizumab (400 mg) were administered as intravenous infusion on day 1 every 3 weeks. Capecitabine was given orally in appropriate dose divided into two split doses for 14 days, followed by 7 days rest, repeated every 3 weeks. In May 2017, after completion of six cycles of systemic CT, partial response of primary RC and lung deposits was confirmed in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. MRI of abdomen and 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 (before was 30 mm, then 14 mm). Chest computed tomography was described as in regression with an unchanged number of lung lesions.

According to 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 concomitant CT. A 50.4 Gy total dose with 1.8 Gy in 28 fractions was given 5 times a week. Concomitant Capecitabine-based CT (825 mg/m2) was administered twice daily, 5 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 CT CAPOX plus Bevacizumab were administrated. Because of adverse events during CT, 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 computed tomography (^{18}F-FDG PET-CT) showed four lung lesions with an increased uptake of radiopharmaceutical, while uptake of pharmaceutical in rectum was not detected (Figure 3). A complete regression of primary tumor was described. Chest and abdomen computed tomography from August 2017 showed stable disease. Pelvis MRI was also performed in August 2017 and revealed complete regression of rectal tumor (Figure 4).

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

Chest-abdomen-pelvis computed tomography 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 DFS period of three years. The treatment had improved 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 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 more developed collaboration between multidisciplinary teams and led to progress in survival rate and median survival duration [10, 11, 12]. According to European Society for Medical Oncology (ESMO) consensus guidelines, a patient with mCRC may reach an overall survival of 30 months as a result of a multidisciplinary decision planned treatment [11, 13]. Nevertheless, the median overall survival in patients with mCRC has increased and it's been reaching over 40 months in molecularly selected patients [4]. Previously published randomized phase III study that evaluated the use of Bevacizumab in combination with Oxaliplatin-based CT as 1st-line therapy in mCRC, had shown that the use of Bevacizumab to Oxaliplatin CT had 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 needed 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., 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 depends also 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 CT 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].

The T. H. van Dijk et al. study 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 [16].

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 5-year survival for mCRC patients with liver metastases who underwent surgical treatment reaches up to 58%, whereas the survival rate for mCRC patients with liver

metastasis without surgical treatment ranges from 20-24 months [18, 19]. Pulmonary resection for metastases from CRC may improve survival in selected patients, thus the outcome may vary of the timing of surgical treatment [20]. Yamada K. et al., showed that follow-up for 9 months from the date of pulmonary metastasy 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.

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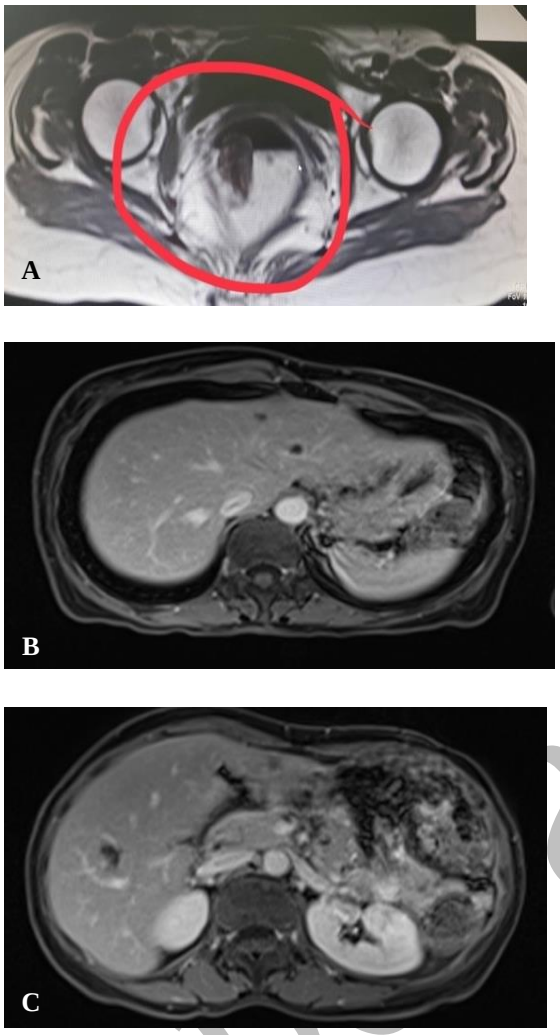

Figure 1. Initial magnetic resonance imaging of abdomen and pelvis in the axial plane showing: (A) on post-contrast T1w sequence, a tumor mass located in rectum, penetrating all layers of the poster wall and infiltrating perirectal fat up to 30 mm, expanding to the mesorectal fascia bilaterally (mrT3d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

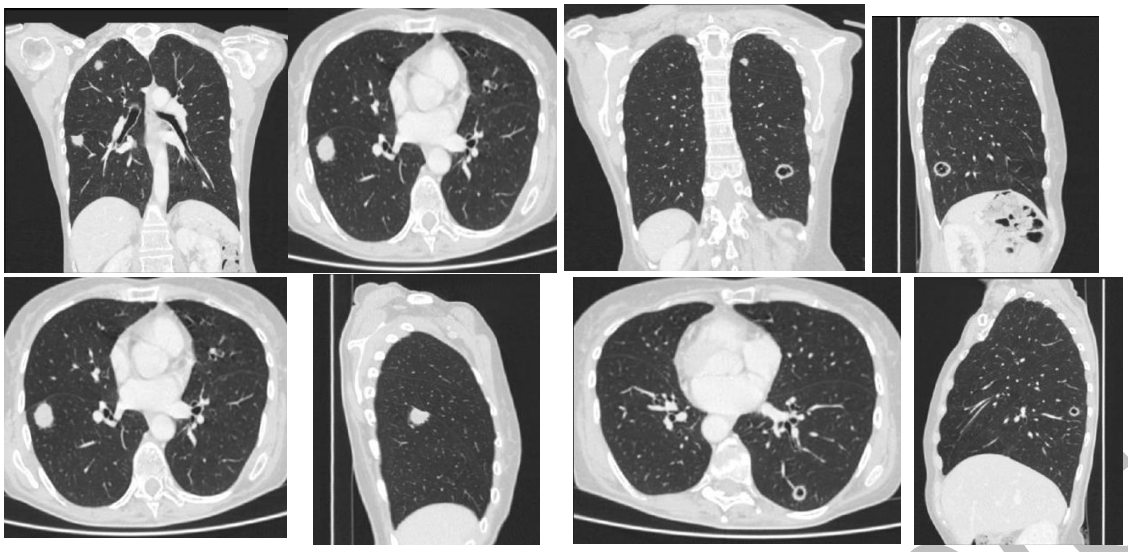

Figure 2. Initial contrast-enhanced chest computed tomography in the axial, coronal and sagittal planes showing multiple nodular and excavated nodular lesions in both lungs: in the apical segment of the upper right lobe 12 mm, in the apicoposterior segment of the upper left lobe 11 mm, in the anterior 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

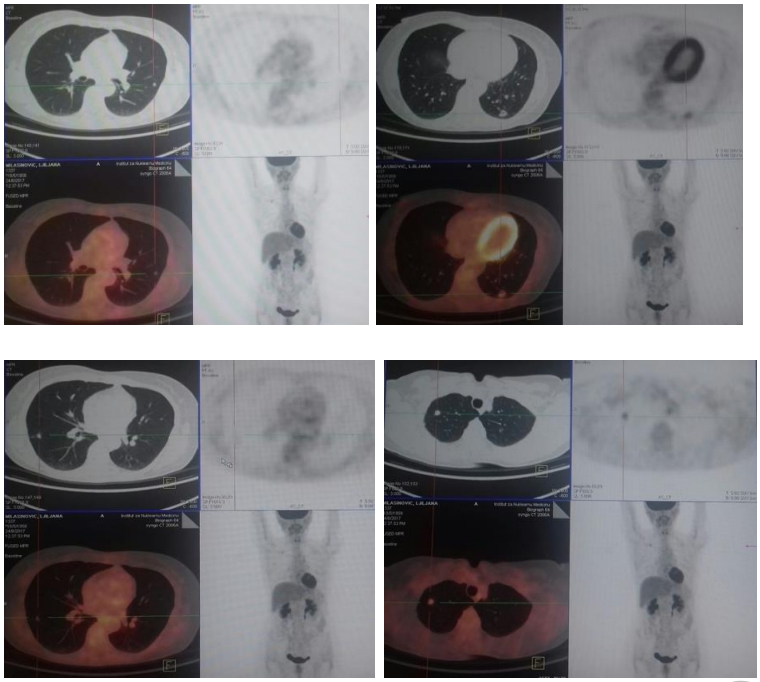

Figure 3. 18F-FDG positron emission computed tomography scans in the axial and coronal planes after systemic chemotherapy, demonstrating four nodular lung lesions with an increased uptake of radiopharmaceutical

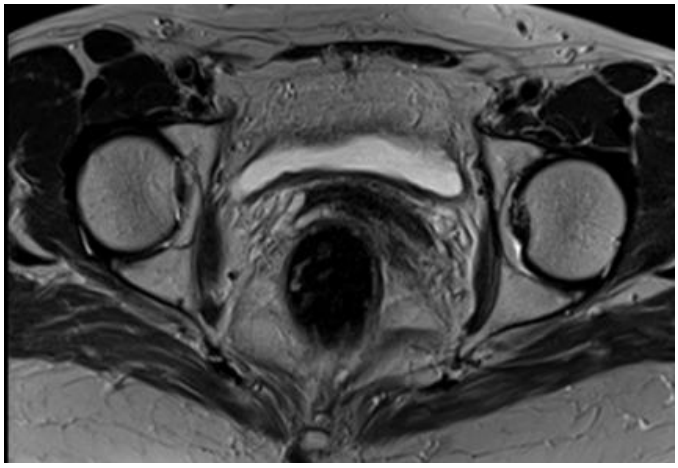

Figure 4. Magnetic resonance imaging of the pelvis after chemoradiotherapy of rectal cancer, in axial T2w sequence demonstrating complete regression of rectal tumor

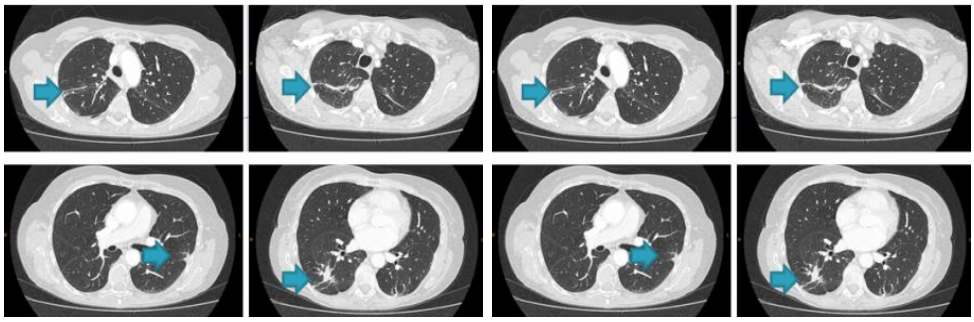

Figure 5. Chest computed tomography in axial planes after lung metastasectomy demonstrating no signs of metastatic recurrence; only fibrotic changes are visible

