Case report

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PREOPERATIVE RADIOTHERAPY IN ESOPHAGEAL CANCER: A CASE REPORT

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Carcinoma of the esophagus is a relatively rare tumor, accounting for 1.5% of overall cancer morbidity. Throughout the world, 480,000 people are affected by the disease each year and men twice as often as women, causing about 400,000 deaths a year.

Most cases are reported in underdeveloped environments, among the middle-aged or elderly. Smoking, excessive alcohol consumption, deficiencies of some dietary microelements and vitamins are among the principal risk factors for the disease. The main symptoms of the disease are progressive dysphagia and dyspepsia, while pain, hoarseness, and cough are common in more advanced disease stages. The diagnosis is established on the basis of histopathology confirmation of the disease from the biopsied material sampled by way of esophagogastroscopy or from the material obtained by way of endoscopic resection. The therapy used in the treatment of esophagus cancers is multidisciplinary. The most common is surgery, radiotherapy, and chemotherapy. Often, these three basic forms of therapy are combined. In this case report, the neoadjuvant therapy consisting of chemotherapy according to the PF protocol and transcutaneous radiotherapy gave an extremely good therapeutic response, and the disease from an unresponsive state was converted into a state of radical operability.

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Key words: *esophageal cancer, multimodality treatment, radiotherapy, preoperative therapy*

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Introduction

Carcinoma of the esophagus is a relatively rare tumor, accounting for 1.5% of overall cancer morbidity. Throughout the world, 480,000 people are affected by the disease each year and men twice as often as women, causing about 400,000 deaths a year (1). Most cases are reported in underdeveloped environments, among the middle-aged or elderly (average age at onset, 59.5 years). Smoking, excessive alcohol consumption, deficiencies of some dietary microelements and vitamins (selenium, vitamin E, beta-carotene) are among the principal risk factors for the disease. Individuals with certain diseases and conditions also have an increased risk for the disease, such as *tylosis palmaris*, severe dysplasia in Barrett's esophagus, untreated achalasia and celiac disease (2, 3). Radiation to the mediastinum (in breast or lung cancer, for instance) also carries an increased risk, similar to the strictures occurring after caustic injuries, and association of esophageal cancer with human papillomavirus has also been reported (1, 4).

Two most common histopathological forms of esophageal carcinoma are planocellular and adenocarcinoma forms (5). Starting from the upper to the lower esophageal portions, the incidence of planocellular type is decreasing, with adenocarcinoma being more and more common (originating from the superficial and deep esophageal glands, embryonic remnants of the glandular epithelium and metaplastic glandular epithelium) (5, 6).

The main symptoms of the disease are progressive dysphagia (in 80-90%) and dyspepsia, isolated or associated with difficulty swallowing. Pain, hoarseness, and dry cough are common in more advanced disease stages, as well as bleeding when other adjacent organs become infiltrated (7). The diagnosis is made based on histopathology confirmation of the disease from the biopsied material sampled by way of esophagogastroscopy or from the material obtained by way of endoscopic resection. Biopsy of multiple sites (usually 6-8) in the changed portion of the esophagus is usually recom-

mended (8). Histopathological classification of the World Health Organization (2010) is used (9). Endoscopic ultrasound, chest x-ray, chest and upper abdomen CT, and PET CT scanning are useful in the assessment of disease spread.

The initial treatment plan for these patients should be formulated at a multidisciplinary tumor board, basing the decision not only upon scientific evidence, but also the aspects present in each individual patient, taking into account his general health condition and existing comorbidities. The tumor board should involve a gastroenterologist, pathologist, radiologist, thoracic surgeon, oncologist, radiation oncologist and, as required, nutritionist and psychiatrist.

Case report

We report a male 68-year-old patient in whom the complaints appeared in January 2018 with difficult swallowing of solid foods. These difficulties progressively worsened in the following few months, with the patient losing 9 kg in body weight (until June 2018).

He consulted a doctor for the first time in April 2018, when esophagogastroduodenoscopy (EGDS) was performed at the Clinic of Gastroenterology and the visualized change was biopsied. The definitive diagnosis was made at the Clinical Center Niš Center for Pathology, and the change was identified as carcinoma squamocellulare partim kerathodes invasivum oesophagei HG II, NG II-III. At the MSCT finding from May 2018, the distal esophagus with an infiltrative tumor change was seen, measuring up to 36 mm in axial diameter and up to 48 mm in craniocaudal diameter, with scarce post-contrast enhancement. In the same month, bronchoscopy was done as well, with no endoscopic abnormalities detected. In that period, the patient was referred to the Clinical Center of Serbia (in Belgrade), Department for Esophageal Malignancies, for a consultancy examination, where the tumor board decision was made, after thorough clinical and laboratory evaluations (with x-ray, ultrasound and MSCT), that the patient should receive neoadjuvant chemoradiotherapy in a regional center. During this hospitalization, a control MSCT scanning of the thorax and abdomen was done, visualizing two nodular lesions in the lung parenchyma, measuring in diameter 5 mm (at the interface of the lateral and medial segment of the middle lobe, on the right) and 2 mm (anterobasal, on the right), which were not highly suspicious for secondary deposits, so that only surveillance of these was then recommended. The thoracic esophagus extended from the level of the ostium of the inferior vena cava caudally for 6.7 cm of tumorously enlarged wall, with the largest axial diameter of 20x25 mm and largest infiltration thickness of about 11 mm, without any signs of infiltration of adjacent structures on CT scanning. It seemed that cardia was not involved with tumor. In the fifth group of mediastinal lymph nodes, several lymph nodes measuring in diameter up to 7 mm could be seen. There were no signs of lymphadenopathy. A solitary focal lesion involving the corpus of Th12 was detected as well, which could not be seen on a repeated control examination. The findings in other structures, as visualized by CT scanning, were without any abnormalities. The decision concerning neoadjuvant chemoradiation was confirmed after the tumor board at the Clinic of Gastroenterology, Clinical Center Niš, in June 2018. The patient received one chemotherapy cycle according to the PF protocol (cisplatin plus 5-fluorouracil) and two cycles of chemotherapy by the PF protocol with radiation therapy of 45 Gy TD in 25 fractions (chemopotentiation).

The patient tolerated well his neoadjuvant chemoradiation treatment, and a month after the completion of planned therapy, a control MSCT scanning of the thorax and abdomen was done at the Clinic of Oncology, Clinical Center Niš, Department of Radiation Therapy, in order to assess the treatment response. At MSCT scanning, a slower passage of peroral contrast medium could be seen, with a stenosis of irregular luminal contours of the distal part of the thoracic esophageal portion, measuring 38 mm in craniocaudal diameter and 27 mm in the axial slice. The findings in other structures, as visualized by CT, were without abnormalities, which suggested disease remission. The patient was then referred to the Clinical Center of Serbia, Department for Esophageal Malignancies, so that possible surgical treatment could be considered. After an adequate preoperative preparation, the patient was surgically treated two months after the completion of his oncological treatment. A "minimally invasive Ivor Lewis" procedure was done (oesophagectomia subtotalis, lymphadenectomia mediastini posterioris, medialis et inferioris et oesophagogastroplasticam per thoracoscopiam et laparoscopiam; explorative thoracoscopy; laparoscopy). Histopathological verification was done at the Department of Pathology, Clinical Center of Serbia - Oesophagitis fibrosa segmentalis chronica postiradiatione sine tumoris, T0, N0 (0/19) Mx L0 V0 PN0. Complete regression (TR 1/5, RCRG 1/3).

Postoperative MSCT findings two months later confirmed the observed postoperative status, with a massive pleural effusion on the left, with compressive atelectasis of the lower lobe on the left. However, tumor cells were not found in the pleural puncture fluid; instead, the presence of lymphocytes and lipoprotein masses were seen (December, 2018; Center for Pathology, Niš). The patient was then presented at the tumor board for oncology in Niš, where the decision was made, on the basis of a satisfactory response to chemoradiation, that specific oncological treatment was not required; regular control visits to his surgeon were recommended.

The patient visited his surgeon in January 2019, two and a half months after the above mentioned interventions, feeling subjectively well, gaining 2 kg in body weight. The next control visit was scheduled for April 2019, and at that visit thoracic and abdominal CT showed pulmonary parenchyma without secondary deposits, with the presence of free fluid basally on the left (up to 6 HU, indicating a transudate), esophageal stump with preserved

lumen and without any apparent recurrence. The anastomosis and most part of the stomach presented mediastinally without any apparent recurrence. Lymph nodes could be seen para-aortally, measuring up to 7 mm. Osseous parts of the thorax were without any visible infiltrations. Abdominal findings were without any abnormality. Laboratory and biochemical parameters were within reference ranges, and tumor marker values were as follows: CEA: 3.8 ug/L; CA 19-9: 5.5 ku/L; and CA 72-4: 1.1 U/mL, which, in addition to other evaluation tests and methods, indicated a complete disease remission. The patient denied having any pains or problems with digestion, and had regular stools and urination, stating that he had gained 10 kg in body weight since the operation.

Discussion

According to the TNM classification, our patient was classified as T3 N0 M0, and as a potentially resectable case received neoadjuvant therapy: one cycle of chemotherapy by PF protocol, and was further treated with chemoradiation, with chemotherapy potentiated by radiation (chemopotentiation). The degree of tumor response to therapy was excellent in our patient, since viable tumor cells could not be demonstrated in the operative material. The degree of tumor response to neoadjuvant therapy, according to the College of American Pathologist classification, was estimated as a complete tumor response and thus belonged to stage 0 (10).

Although carcinoma of the esophagus belongs to the group of chemoresistant tumors, the success of therapy was significantly influenced by concomitant chemo- and radiation therapy. Chemotherapy preceding the combined approach was the same as that used in combination with radiation. Cisplatin and 5-fluorouracil (PF protocol) are the agents commonly used. The first cycle is administered four weeks before the beginning of radiation. Cisplatin is given on the first day of the cycle at a dose of 100 mg/m^2, while 5-fluorouracil is given as a 24-hour infusion at a dose of 1000 mg/m^2, from days 1 to 5 of the chemotherapy cycle. After the first cycle, radiation therapy is introduced. Transcutaneous therapy of esophageal cancer is administered on the linear accelerator "Electa", using high-energy x-rays (10 MeV or more) and with three radiation portals. As a standard, the patient is irradiated in supination, with hands raised above the head, using the appropriate radiotherapeutic accessories. The dose of 45 Gy in 25 fractions is administered to the tumor tissue, using 3D conformal radiation technique, taking into account radiosensitivity of high-risk anatomical structures (spinal cord, healthy lung, heart, pericardium) (Figure 1, 2). ICRU 50 and supplement ICRU 62 were used in the contouring of target volumes. During the radiation therapy, for the purpose of reproducibility, radiotherapy portal precision check-ups were done each week. During the treatment, there were no significant adverse effects.

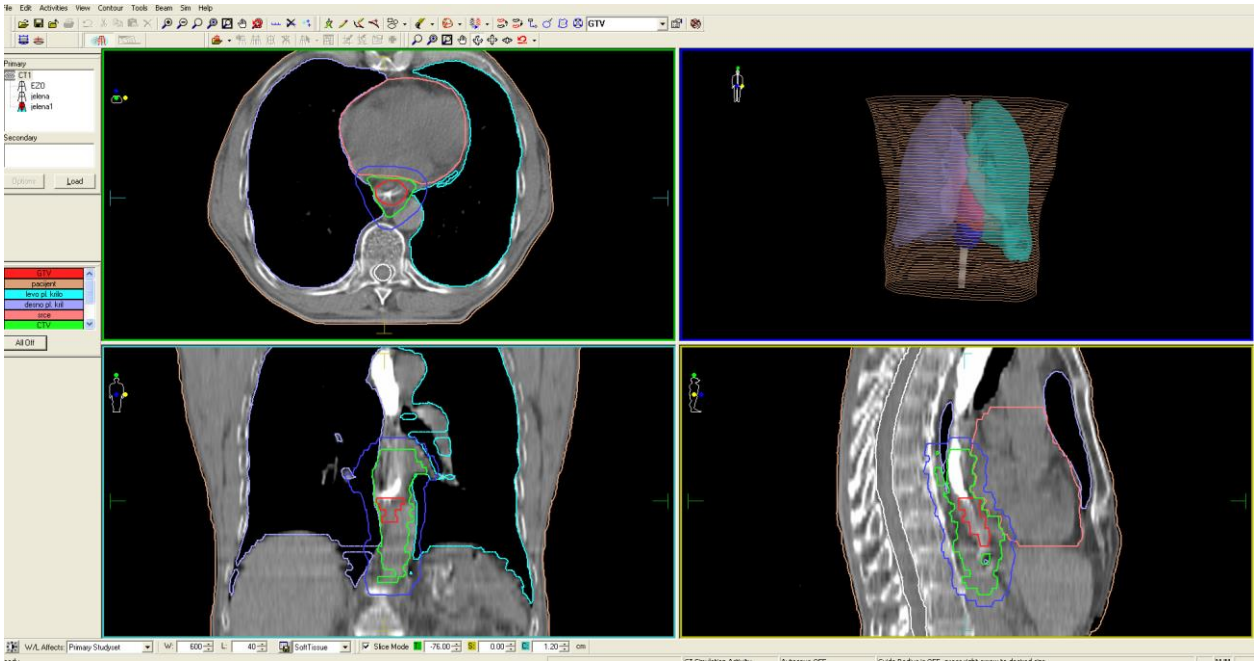

Figure 1. Presentation of delination of target volumens and organs of risk (3DCRT), neoadjuvant (chemo) radiotherapy for oesophageal cancer

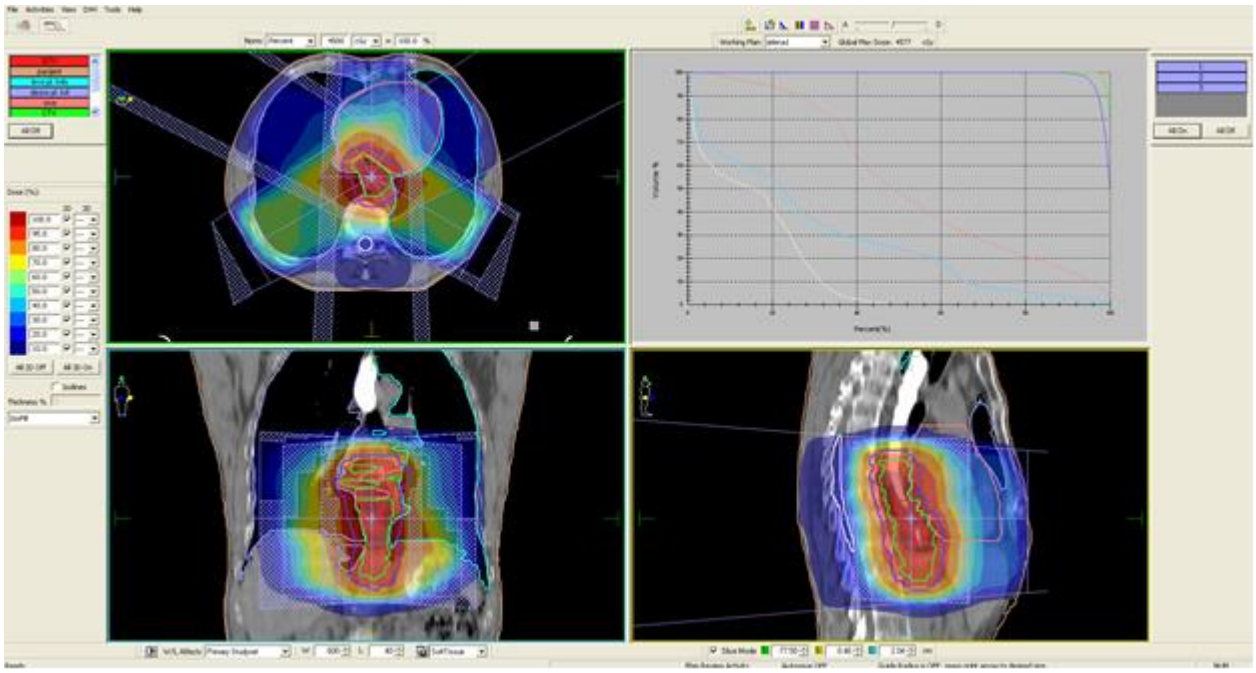

Figure 2. Dose distribution and field arrangement in 3D conformal preoperative radiotherapy for oesophageal cancer ("mercedes" technique)

Thanks to an excellent therapeutic response to chemoradiation, the treatment was continued in the Clinical Center of Serbia, where the surgical procedure was performed. Surgical therapy is the therapy of choice for patients with limited disease, i.e. those with lower disease stages (0, I, IIA, IIB). Although the disease is operable in these stages, a significantly prolonged survival period has been observed in patients with *in situ* disease (11). Neoadjuvant chemoradiation followed by surgical resection is the treatment option for both histopathological tumor forms in locally advanced stage of esophageal cancer, as is the case with the patient we are presenting (12). Postoperative chemotherapy has yielded therapeutic effects in patients with esophageal adenocarcinoma localized in the lower third of the esophagus, while for the disease involving other portions of the esophagus and in planocellular carcinoma cases these effects have not been observed (13). According to the results published so far in the literature, the use of postoperative radiotherapy in cases with positive resection margins results in better local disease control rates, but it affects overall survival rates as well (14). In patients with advanced disease, the only treatment modality is palliative radiation therapy, aiming to improve the act of swallowing and to alleviate pain (15, 16).

Since R0 resection was histologically confirmed, as well as the fibrosis of resected change, the patient was relocated from a potentially incurable condition to the category of potentially curable patients. Taking into account that 5-year survival of patients with esophageal cancer is 17.9% according to most studies, we consider that the treatment of this patient was very successful and that there is a possibility that the patient would enjoy a longer period without disease relapse.

Conclusion

Our patient was treated with neoadjuvant therapy in accordance with the tumor board decision and was relocated from the category of unresectable to the category of resectable disease. Neoadjuvant therapy, involving chemotherapy by the PF protocol and transcutaneous radiation therapy, yielded an excellent therapeutic response. Chemoradiation produced in this case a complete pathological response, so that the patient could be radically treated by surgery. It can be seen from our report that radiation therapy significantly contributed to the success of treatment of this patient. We expect that with further advancements in the domains of equipment and radiation techniques we will be in the position to offer to these patients intraluminal brachytherapy as well.

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PREOPERATIVNA RADIOTERAPIJA KARCINOMA JEDNJAKA: PRIKAZ SLUČAJA

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Karcinom jednjaka je relativno redak tumor i u ukupnom morbiditetu učestvuje sa 1,5%. Svake godine u svetu oboli oko 480.000 ljudi, među kojima je veći broj muškaraca u odnosu na žene, a oko 400.000 obolelih godišnje ima letalan ishod. Većina slučajeva registruje se u manje razvijenim sredinama, u srednjoj i starijoj životnoj dobi. U osnovne faktore rizika ubrajaju se pušenje, prekomerno konzumiranje alkohola, deficit pojedinih mikroelemenata i vitamina u ishrani. Osnovni simptomi su: progredijentna disfagija, dispepsija, dok se bol, promuklost i nadražajni kašalj, javljaju u odmaklim stadijumima bolesti. Dijagnoza se postavlja na temelju patohistološke potvrde bolesti iz biopsiranog materijala uzetog ezofagogastroskopijom ili iz materijala dobijenog endoskopskom resekcijom. Terapija koja se primenjuje u lečenju karcinoma ezofagusa je multidisciplinarna. Najčešće je reč o hiruškoj, i zračnoj terapiji, kao i hemioterapija. Često se ova tri osnovna vida terapije kombinuju. U ovom prikazu, neoadjuvantna terapija, koja se sastojala iz hemoterapije po PF protokolu i transkutane radioterapije, dala je izuzetno dobar terapijski odgovor, pa je bolest iz neresektabilnog stanja prevedena u stanje radikalne operabilnosti.

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Ključne reči: *karcinom jednjaka, multidisciplinarni tretman, radioterapija, preoperativna terapija*