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ADVANCEMENTS IN RECTAL CANCER TREATMENT: THE ROLE OF SHORT-COURSE RADIOTHERAPY-COMPREHENSIVE OVERVIEW

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Summary

Rectal cancer is a disease in which malignant cells form in the epithelium of the rectum. Symptoms of rectal cancer are changes in bowel habits or blood in stool. It is curable, especially if detected early. Patients undergo treatment that includes surgery, chemotherapy, and radiotherapy. Radiotherapy uses energy sources to eliminate cancer cells. Short-course radiotherapy (SCRT) is a neoadjuvant form of treatment for resectable cancer consisting of five radiation fractions of five Grays delivered over five days and surgery performed the following week. Advances in treatment regimens over the last few decades have improved survival rates of rectal cancer.

KEYWORDS: *rectal cancer; short-course radiotherapy; neoadjuvant therapy*

INTRODUCTION

Rectal cancer, a prevalent malignancy worldwide, represents a significant challenge in oncology due to its unique anatomical location and the complexity of treatment. Rectal cancer is the third most common cancer in the world, and thirty percent of all colon cancers develop in the rectum. Historically, the management of rectal cancer has evolved dramatically, with significant strides made in diagnostic, surgical, and radiation therapies. In the last 30 years, we have witnessed significant advances in detecting and treating rectal cancer, mainly based on improvements in diagnostics and preoperative disease classification, surgical techniques, and histopathological evaluation of the resected sample. The primary diagnostic tool for the preoperative assessment of the disease is magnetic resonance imaging due to its ability to accurately depict the mesorectal fascia (MRF) and determine tumor infiltration(1). Patients whose cancer is detected at an early stage can be adequately treated only with surgery. However, a significant proportion of patients with rectal cancer have locally advanced disease and will potentially benefit from tumor reduction before surgery, which is achieved by neoadjuvant treatment, which includes radiotherapy and chemotherapy, used alone or concomitantly with radiotherapy(2).

In recent years, short-course radiotherapy (SCRT) has emerged as a pivotal element in the treatment paradigm, balancing efficacy and patient quality of life. There are two ways of delivering radiotherapy that has been researched over the past years: short-course radiotherapy that de-

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livers 25 Gy in five fractions over five days, immediately followed by surgery, and long-course radiotherapy that delivers 40- 50 Gy in 20 to 25 fractions over 4 to 5 weeks followed by surgery 4 to 6 weeks later. Regardless of the protocol, the role of radiotherapy in the treatment of locally advanced rectal cancer has been established, with evidence showing that patients undergoing preoperative radiotherapy have a significant reduction in local recurrence rates of 50 to 60% compared with surgery alone. The current gold standard for the treatment of advanced rectal cancer is, therefore (chemo)radiotherapy followed by surgical excision, and the prognosis is directly related to tumor infiltration into the mesorectum and the ability to surgically achieve a negative circumferential resection margin (CRM).

UNDERSTANDING RECTAL CANCER

Rectal cancer arises in the rectum, the final section of the large intestine, and poses unique challenges due to its proximity to vital structures within the pelvic area. This cancer type is often characterized by its aggressive nature and potential to metastasize, making early detection and effective treatment crucial for patient survival. Colon cancer is the third most common cancer in the world, and in Croatia, it is the most common malignant disease. According to data from 2020, there were an estimated 1.9 million cases of rectal cancer in the world, of which 0.9 million died. Of these, 515,367 were men and 419,536 were women(3). This figure is predicted to increase to 3.2 million by 2040(3). Colon cancer ranks second in terms of mortality in Croatia, right behind lung cancer. The frequency is higher in highly developed countries, and it is also increasing in medium-developed countries. The increase in incidence is mainly attributed to increased exposure to environmental risk factors resulting from changes in lifestyle and diet(4). In 2020, Croatia ranked 10th in the world with 36.3 cases per 100,000 people(3). The main risk factor for rectal cancer is age: after the fifth decade of life, the risk is highly increased, while under the age of fifty, it is scarce (except for hereditary cancers)(5). Sporadic cases of rectal cancer without a family history account for 60-65% of all cases, and it is most often attributed to acquired somatic genetic mutations or changes caused by variable risk factors(6). The risk of rectal cancer in patients with inflammatory bowel disease is 2.4 times higher than in healthy subjects(7), the risk of patients with ulcerative colitis is increased by 3.7%(8), and in people who have Crohn's disease 2, 5%(9).

Rectal cancer is greatly influenced by low physical activity, poor diet, excessive alcohol intake, smoking, and obesity. The risk of rectal cancer in obese men is 25 to 50% higher than in men of normal weight(3). Also, a high intake of processed foods, red meat, refined carbohydrates, and a diet with a low calcium content facilitates the inflammatory response and increases the risk of rectal cancer. Furthermore, smoking has also been shown to be an established factor, given that the components of tobacco smoke damage the mucosa of the colon and cause further genetic or epigenetic changes. Current smokers show poorer survival from rectal cancer than non-smokers(3).

EVOLVING TREATMENT LANDSCAPE

The primary diagnostic method in the diagnosis of rectal cancer is endoscopy with biopsy. It enables tumor localization and biopsy, i.e., taking a piece of the large intestine for histological examination. Furthermore, rectal cancer diagnostic methods include taking anamnesis, clinical examination, complete blood count, biochemical blood tests, and tumor markers. Recently, non-invasive virtual colonoscopy has been increasingly used to obtain 2D and 3D images of the colon, which are used for analysis and performed on a CT machine.

Traditionally, the treatment of rectal cancer involved extensive surgical procedures, often resulting in significant morbidity and altered patient quality of life. The surgeon removes the part of the rectum affected by the tumor, as well as the edge of healthy tissue around it. It also removes the fatty tissue (mesorectum) around it due to the possibility of cancer cells spreading to it, and it is a layer of tissue that surrounds the intestine and rectum and contains blood vessels and lymph nodes. This operation reduces the risk of recurrence, and there are different types of complete mesorectal excision depending on where the cancer is located and how big it is(10). Front or anterior resection (LAR) resects the sigmoid colon and rectum with the mesorectum and mesosygmum.

The cut ends of the intestine are rejoined, and the newly formed joint is called an anastomosis. Nowadays, anastomosis is most often performed using a stapler due to the speed of performance and the easier performance of a low anastomosis. Front anterior resection can be upper (when the colorectal anastomosis is performed on the intraperitoneal part of the rectum) and lower (when the anastomosis is performed in the subperitoneal part of the rectum). This technique is also called Dixon's operation after Claude F. Dixon developed this modern technique(11).

Abdominoperineal rectal resection (APR) (resection according to Miles) is used when the cancer is located low, i.e., up to 5 cm from the anocutaneous border and when the tumor enters the anal sphincter or nearby muscles. It removes the entire rectum with the anus and perirectal tissue, part of the parietal peritoneum of the pelvic floor, and the aboral branch of the sigmoid colon with the corresponding mesentery(12). After that, it is necessary to form a permanent colostomy.

Transanal excision (TE) is used for cancers located inside the anal canal and for relatively small cancers. The operation is performed through the anus and removes the tumor and small amounts of surrounding tissue while the anus and sphincter remain intact. So, the advantages of such a procedure are obvious, which is that an incision on the abdominal wall and the creation of an anastomosis are avoided. At the same time, the disadvantage is the impossibility of performing a lymphadenectomy. TE is only suitable for resection of distal tumors because access to proximal rectal lesions is limited.

Resection, according to Hartmann, represents the resection of the sigmoid colon and the upper part of the rectum, but without establishing the continuity of the intestine, and is most often used in ileus, diverticula, and is most often used for palliative purposes. After that, anastomosis is not recommended, but the intestinal opening on the abdominal wall, called a stoma, and the rectal end is closed. Such a condition can be permanent or temporary with the establishment of an anastomosis a few weeks after the operation itself(13).

Regarding minimally invasive surgery, in 1983, Professor Gherard Buess described transanal endoscopic microsurgery (TEM) for the resection of low rectal lesions. It represents a safe and effective method of treating rectal cancer in an early stage. This minimally invasive technique offers the advantages of superior visualization of the tumor using special equipment that enters through the anal canal, and the entire procedure is monitored on a monitor. Specialized equipment enables access to tumors up to 24 cm from the anal edge and greater precision of resection.

Recovery time is much shorter than classic surgical procedures and has lower long-term recurrence rates than transanal excision(14). The main limitation is the requirement for expensive and highly specialized equipment. However, the last few decades have shifted towards more conservative and targeted approaches. One is a combination of radiotherapy and total mesorectal excision, improving disease control. However, since it is still not effectively solved, patients still die from metastatic disease(15). Key among these is the introduction of Short-Course Radiotherapy (SCRT), a treatment modality that has significantly transformed the rectal cancer treatment landscape.

THE EMERGENCE OF SCRT

SCRT, involving a concise and intensive course of radiation therapy, typically delivered over five days, followed by surgical intervention, has become increasingly popular. Radiotherapy aims to destroy tumor cells, thereby controlling tumor growth and stopping the spread of ionizing radiation to the surrounding healthy tissue.

During radiation, the dose received by the surrounding healthy tissue (especially the organs at risk) should be as small as possible since it can cause pathological changes in the same with irreversible damage(16).

To reduce the initial tumor volume and improve local disease control, preoperative or neoadjuvant radiotherapy is used(17). It can be delivered in two forms. The first form of neoadjuvant radiotherapy is called long-course radiotherapy, in which 40 to 50 Gy is delivered in 20 to 25 fractions over 4 to 5 weeks, followed by surgery 4 to 6 weeks later. Another form is called short-course radiotherapy, in which 25 Gy is delivered in 5 fractions over one week, immediately followed by surgery. Regardless of which protocol is chosen, preoperative radiotherapy reduces the incidence of local recurrence by 50 to 60% compared to sur-

gery(17). Neoadjuvant radiotherapy is combined with chemotherapy that includes fluoropyrimidines, most often oral capecitabine. A randomized clinical trial showed that short-course neoadjuvant RT is more effective and less toxic than adjuvant long-course RT. In the trial, significantly fewer local recurrences (13% vs. 22%) were observed in patients who underwent short-course RT compared to those who underwent adjuvant long-course RT(18). Also, a meta-analysis of 8 studies with 1475 patients was recently published, comparing short-course and long-course radiotherapy(19). Subgroup analysis showed that the probability of distant metastases was significantly higher in long-course radiotherapy compared to short-course radiotherapy.

Regardless of duration, more studies were conducted to prove the difference in the efficiency of preoperative and postoperative chemoradiotherapy on the patient's outcome(20,21). Sauer et al. noticed that preoperative chemoradiotherapy caused less toxicity compared to postoperative. However, there was no difference in the survival rate(22). To eliminate the impact of timeframe on such results, they monitored the results of the same sample for seven more years(23). The observation was similar to the previous one. Depending on the organ's sensitivity to radiation and the received dose, the organ can be functional or non-functional, and the factors that influence this are the absorbed dose received by the entire organ and the volume of the organ at risk that received a specific dose(22). The radiotherapy process begins with a scan of the patient, i.e., a CT simulation, and the purpose is to determine the exact location, shape, and size of the tumor or the tumor bed if it has been surgically removed. The resulting CT scan must contain all organs and structures between the second lumbar vertebra and half of the femur, with a scan thickness of 3 mm. Target volumes are outlined to distribute the absorbed dose to the tumor and the surrounding healthy tissue. There are three main volumes in radiotherapy planning. The first volume is the Gross Tumour Volume (GTV), which is visible and indicates the location of the malignant growth. It also includes the surrounding lymph nodes (if they are affected by a tumor). If the cancer has been surgically removed, the tumor site is marked with GTV. The second volume contains the GTV and a margin for the subclinical spread of a disease considered to be treatable and is called the Clinical Tumour Volume (CTV). It represents the true extent and location of the tumor. Delineation of the CTV assumes no tumor cells outside this volume and must receive an adequate dose to achieve the therapeutic goal. The third volume is the Planning Target Volume (PTV), and it allows for uncertainties in the planning and execution of the treatment itself in such a way as to set a margin around the CTV that is large enough to compensate for unconscious movements, such as breathing and conscious patient movement(23).

Radiotherapy techniques for the treatment of advanced rectal cancer (LARC) have significantly developed in recent years. The transition from 3D CRT to IMRT and VMAT has led to a more precise dose conformation and, consequently, more effectively spared organs from risk. Using IGRT, i.e., image-guided radiotherapy, it is possible to reduce the dose of OAR by creating steep dose gradients between the tumor and the surrounding healthy tissu(24). IGRT methods include electronic portal imaging devices (EPID) and cone beam computed tomography (CBCT). EPID provides high-quality localization images and computer-aided analysis. EPID has been proven to be a powerful tool for reducing errors during treatment and for quality assurance and verification of complex treatments by comparing the portal image obtained during treatment with a reference CT scan, called a digitally reconstructed radiogram, DRR.

Recordings are made in two projections, AP and LL. In this way, possible errors during adjustment are corrected. However, hardware, software, and integration are also some limitations. The size of the EPID image detector covers a maximum of a 30x25 cm2 field at the isocenter for most commercial systems. Imaging a more extensive field would require acquiring multiple images using detectors at different locations and digitally adding them together. However, this function is not yet commercially available(25).

A more modern method used for correct patient positioning is CBCT, which allows radiological technologists to correct errors and provides insight into soft tissue structures, localization of the target volume, and organs at risk. After positioning the patient in the intended position, the CBCT makes all or part of a circle around him and thus creates a single CT image. Images produced

by kilovolt CBCT show high resolution due to the dominance of the photoelectric effect at kilovolt energies. The reconstructed CBCT image is compared with the reference CT image used to create the plan, a fusion is made, and the system automatically corrects the resulting shift(26).

BENEFITS OF SCRT IN RECTAL CANCER TREATMENT

The primary advantage of SCRT lies in its ability to reduce tumor size effectively, thereby facilitating less invasive surgical procedures. Additionally, its shorter treatment duration is more convenient for patients, reducing the overall burden of cancer treatment. Studies have shown that SCRT can improve local disease control and decrease the likelihood of cancer recurrence. SCRT is often part of a multimodal treatment strategy combined with chemotherapy and advanced surgical techniques. This integrated approach is tailored to each patient's specific cancer stage and overall health, optimizing treatment outcomes and preserving as much normal function as possible. In a clinical study by Kapiteijn et al.(27), 1,805 patients were followed and were divided into two groups. The first group received short-course radiotherapy and underwent surgery, while the second group only underwent surgery. Following the results over two years, the local recurrence rate of the first group was 2.4%, and the second group was 8.2% ($p<0.001$). The percentage of recurrence for the first group coincides with our research, and we can conclude that short-course neoadjuvant radiotherapy with surgery reduces the risk of local recurrence.

The RAPIDO clinical trial randomized patients with high-risk locally advanced rectal cancer into two groups. The first, experimental, received short-course radiotherapy followed by preoperative chemotherapy, and the second, long-course chemoradiotherapy with optional adjuvant chemotherapy. A three-year follow-up showed a lower percentage of relapses in the experimental group (23.7% vs. 30.4%) and a reduction in metastases (20% vs. 26.8%)(28). This approach contrasts with the traditional long-course radiotherapy, offering the benefits of reduced treatment duration and a potentially lower incidence of side effects.

CHALLENGES AND FUTURE DIRECTIONS IN SCRT

While SCRT offers numerous benefits, it has challenges. The timing of surgery following SCRT, the patient's response to radiation, and the potential long-term effects on bowel function are areas of ongoing research and consideration. The most common side effects of radiotherapy for rectal cancer occur in the hematopoietic, digestive, and urogenital systems. Leukopenia and thrombocytopenia can occur most often, which are more common with chemoradiotherapy. For these reasons, the blood count is checked every week. Gastrointestinal side effects are manifested by loss of appetite, nausea and vomiting, abdominal pain, and diarrhea. In milder cases, patients can be treated with fluid and electrolyte replacement, antiemetics, or antispasmodics, while in more severe cases, doctors must stop radiotherapy or adjust the radiation plan(29).

Rectal side effects are most often manifested by tenesmus, painful stool, and the appearance of mucus in the stool. People in these cases should reduce rectal irritation, avoid constipation, and ensure an adequate supply of nutrients and water. Late side effects occur 3-6 months after the end of radiotherapy and are more challenging to treat: include chronic radiation proctitis, which represents inflammation and damage to the lower parts of the colon, bleeding, rectal or anal strictures.

In the urogenital system, early reactions that can occur are cystitis, urethritis, and painful urination. Most of the symptoms are mild, and the condition is eased by drinking more water and using antispasmodics. Chronic side effects are hemorrhagic cystitis, urethral stricture, etc. Some patients have sexual dysfunction after radiotherapy, which is associated with damage to blood vessels and nerves caused by radiotherapy and surgery(30).

Looking ahead, the treatment of rectal cancer is moving towards more personalized approaches. Advances in genetic and molecular profiling of tumors enable the development of tailored treatment strategies, focusing on maximizing efficacy while minimizing adverse effects.

DISCUSSION

Rectal cancer is one of the most common malignant neoplasms in humans and the third most

common cancer in the world. During the last few years, the diagnosis and treatment of rectal tumors, as a separate entity from other parts of the colon, has been greatly developed. With the help of advanced imaging techniques, these cancers can be diagnosed at earlier stages. Various studies looked at the demographic characteristics of colon cancer and concluded that the incidence is higher in men than in women. In more developed at the time of disease diagnosis, the median life expectancy is 70 years(31). The journey of rectal cancer treatment, from extensive surgeries to innovative approaches like SCRT, illustrates the progress in oncology. Each year, treatment with this technique was more frequent (in 2014, 3 patients; in 2015 and 2016, 4 patients; in 2017, 7 patients; in 2018, 9 patients; in 2019, 11; in 2020, 14, and after 2021, the number again fell to 18 patients). Moreover, many studies have demonstrated the importance of CRM as an independent prognostic factor for local recurrence and long-term survival, including the first report by Quirke et al.(32).

In conclusion, as research continues to evolve, there is optimism for more effective, personalized treatments, offering hope to rectal cancer patients worldwide.

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Sažetak

NAPREDAK U LIJEČENJU REKTALNOG RAKA: ULOGA KRATKOTRAJNE RADIOTERAPIJE - SVEOBUHVATNI PREGLED

E. Muše, I. Renko, I. Trkulja, M. Mikulandra, A. Vrdoljak, M. Solak

Karcinom rektuma je bolest u kojoj se maligne stanice stvaraju u epitelu rektuma. Simptomi raka rektuma su promjene u crijevnim navikama ili krv u stolici. Izlječiva je, osobito ako se rano otkrije. Pacijenti se podvrgavaju liječenju koje uključuje operaciju, kemoterapiju i radioterapiju. Radioterapija koristi izvore energije, poput X-zraka, za ubijanje stanica raka.

Kratkotrajna radioterapija (SCRT) je neoadjuvantni oblik liječenja resektabilnog raka koji se sastoji od pet frakcija zračenja od pet Graya koji se daju tijekom pet dana i operacije koja se izvodi sljedeći tjedan. Zahvaljujući napretku u liječenju u posljednjih nekoliko desetljeća, stope preživljavanja od karcinoma rektuma značajno su se poboljšale.

KLJUČNE RIJEČI: *karcinom rektuma; short-course radioterapija; neoadjuvantna terapija*