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First-time use of deep hyperthermia in local advanced Colo-rectal cancer: A preliminary insight into its role in improving quality of life and survival time.

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Abstract

Background:

Rectal cancer is a common malignant tumor of the digestive tract, and its morbidity and mortality are increasing yearly. Treatment is mainly based on surgery and chemoradiotherapy, and targeted therapy and immunotherapy are primarily used for locally advanced stages. In this study, we describe a case of rectal cancer with ulcers that gradually healed after local deep hyperthermia combined with chemotherapy. The pain and the local discomfort symptoms were alleviated, and survival and quality of life were improved. This study provides a new clinical treatment model for similar diseases.

Case summary:

A 53-year-old male patient was diagnosed with rectal cancer in August 2020, with a giant cancerous ulcer (10*7 cm) in the anus and perineal region; after 11 cycles of capecitabine plus Oxaliplatin (XELOX) chemotherapy, stable disease (S.D.) was achieved in March 2021. Specialist examination revealed ulcers at the perineum (from the 6 o'clock position of the anus to the coccyx), which showed bulging edges, uneven surfaces, erosion, and bleeding. The mass had poor mobility. Digital rectal examination showed an empty rectum, a complicated ulcer could be palpated in a half-circle of the anal canal at the 6:30 position, the upper pole was located 3.0 cm above the dentate line, and no blood stains were observed on finger cots. Considering the side effects of Oxaliplatin, 10 rounds of local deep hyperthermia were started in April 2021, chemotherapy with capecitabine monotherapy was administered for 2 cycles, and the ulcer area gradually increased. The tumor shrank, and the ulcer surface gradually healed after 10 sessions of hyperthermia.

Conclusion: Local deep hyperthermia combined with chemotherapy can promote gradual healing of ulceration of rectal cancer and improve survival and quality of life.

Keywords: Ulceration of rectal cancer; local deep hyperthermia; chemotherapy; case report

Introduction

The latest research data show that the incidence of colorectal cancer in China is increasing yearly and tends to affect younger individuals and the incidence and mortality of colorectal cancer rank third among malignant tumors **[1]**. The standard treatment model for locally advanced rectal cancer (LARC) is chemoradiotherapy (CRT) or short-course preoperative radiotherapy (SCRT) + total mesorectal excision (TME) + adjuvant chemotherapy. This model has significantly improved the local control of rectal cancer and reduced the 5-year local recurrence rate of total treated cases to 5–10 % **[2]**. In addition, CRT combined with TME causes organ dysfunction (including defecation, urination, and sexual dysfunction), and the organ damage caused by abdominal perineal resection (APR) severely reduces the quality of life of patients. Identifying new treatment methods is an urgent task to reduce the local recurrence rate of colorectal cancer and improve patients' survival and quality of life. The single-treatment mode can no longer meet the clinical treatment needs of tumors, and integrated treatment models, including surgery, radiotherapy and chemotherapy, targeted therapy, natural immunization, and hyperthermia, are gradually developing **[3]**. Surgery, chemoradiotherapy, targeted therapy, and natural immunization are all subject to the limitations of toxicity and side effects. Hyperthermia has gradually emerged in treating malignant tumors and is playing an increasingly important role. **[4]**

Hyperthermia is known as "green therapy," which refers to changes in cell membrane function, structure, and permeability under the action of high temperatures that are conducive to the entry of chemotherapeutic drugs into cancer cells. Meanwhile, hyperthermia can increase the crosslinking of drugs with Deoxyribo Nucleic Acid (DNA), enhance the ability of drugs to kill cancer cells, increase the sensitivity of cancer cells to chemotherapeutic drugs, inhibit the

synthesis and secretion of vascular endothelial growth factors, hinder tumor angiogenesis, and enhance patient immunity **[5]**. Cao L, Chen X, Jia J, et al. **[6]** have shown that hyperthermia can effectively increase the concentration of intravenous chemotherapy drugs in tumor tissues, reducing their toxic side effects and improving their antitumor outcomes. In vitro studies have reported that after heating at 42 ℃ for 2 hours, the antitumor effect of chemotherapeutic drugs can be enhanced by 10- to 100-fold **[7]**. Hyperthermia can significantly increase the local control rate of conventional treatments on tumors and improve long-term survival by traditional therapies and has an incomparable effect with other medicines. Therefore, in 1985, hyperthermia was certified by the U.S. FDA as the fifth primary treatment for tumors after surgery, radiation therapy, chemotherapy, and biological therapy.

A case of rectal cancer with a giant ulcer in the anus and perineal area at the tumor center of the Affiliated Zhongshan Hospital of Dalian University was treated with local deep hyperthermia combined with chemotherapy.

1. Case data

A 53-year-old male patient infected with HPV was admitted to the Proctology Department of Affiliated Zhongshan Hospital of Dalian University in August 2020 due to anal ulceration and bleeding for more than a year. Colonoscopy performed on admission suggested anal canal cancer. A specimen for pathology was collected through the anus, and the results were as follows: 1. Mucinous adenocarcinoma (moderately differentiated) was observed at the perianal area, anal verge, anal canal, and anorectal ring without intraventricular tumor thrombus or nerve invasion. 2. Anal verge and anal anorectal ring skin showed cancer involvement. No indication for surgical resection of the tumor was identified, and the patient was transferred to the cancer center after one year of anal ulceration and bleeding. On August 19, 2020, Oxaliplatin for injection--XELOX chemotherapy was performed for 11 cycles: Oxaliplatin 250 mg get d1 + capecitabine, 1.5g in the morning, 2.0g in the evening P.O. d1-14, Q21d/C. After chemotherapy, symptoms such as grade II gastrointestinal reactions (moderate nausea and diarrhea), grade I bone marrow suppression (mild nausea and diarrhea), heart palpitations, and chest tightness was reported at the end of the cycle. Stable disease (No further aggravation of the condition and maintenance of the state before thermotherapy) was achieved. The date of the last chemotherapy session was March 21, 2021. Genetic testing did not reveal mutated genes **(Table 1, Table 2)**, and targeted therapy was not conducted. The patient's specialist examination in the lithotomy position showed flake ulcers at the perineum (from the 6 o'clock position of the anus to the coccyx), which had bulging edges, uneven surfaces, erosion, and bleeding; the mass was 10.0 × 7.0 cm and had poor mobility. Digital rectal examination showed an empty rectum, a complicated ulcer could be palpated in a half-circle of the anal canal at the 6:30 position, the upper pole was located 3.0 cm above the dentate line, and no blood stains were observed on finger cots. In April 2021, the local deep hyperthermia was performed using an intelligent dynamic energy-focusing targeted hyperthermia system **(Figure 1)** in the Hyperthermia Center of Affiliated Zhongshan Hospital of Dalian University from Monday to Friday once a day for 40 minutes each time at a power of 160 W, with diathermy at a depth of 17 cm; the trajectory was circular, and the lesion temperature was 42–43 °C. The family members signed an informed consent form and a quality of life score sheet for quality of life assessment before the hyperthermia. Considering Oxaliplatin had been used for 11 cycles, allergic reactions can occur; thus, oral capecitabine monotherapy (1.5g in the morning and 2.0g in the evening P.O. d1-14 Q21d/C) was given for 1 cycle. The patient's anal ulceration gradually healed after 8 days of hyperthermia, and fresh granulation tissue began to grow after 10 days. **(Figure 2)**. Defecation pain was relieved, and the mass was significantly smaller than before. The last follow-up date was August 10, 2021. A total of 52 local deep hyperthermia treatments (Last hyperthermia time: June 12, 2021). During the treatment period, tumor markers (CEA, CA724) levels gradually decreased **(Figure 3)**. Repeated pelvic computed tomography (C.T.) showed that the rectal lesion was not significantly reduced in size, but the tumor activity in the lesion was reduced considerably **(Figure 4)**.

Table 1: Genetic testing results

Testing significance	Testing items	Testing results	Clinical Tips
Targeted therapy and prognosis	Clinically significant somatic cell variants	KRAS p.G12D BRAF no pathogenic mutations were detected; NRAS no pathogenic mutations were detected TP53 p.C176Y	(Drug resistance/ Sensitivity reduction/ Sensitive) Sensitive
Immunotherapy efficacy	Microsatellite instability (MSI)	Microsatellite stabilization (MSS)	Lower return
	Mismatch repair genes	pMMR	Lower return
Chemotherapy drug index	Drug metabolism, efficacy, adverse effect assessment	See the chemotherapy section for details	See the chemotherapy section for details
Sample quality control	Overall sample quality assessment	Level A	

Table 2: Variable loci with clinical significance or unclear clinical significance

Genes	Mutation/amplification/fusion/expression	Mutation/fusion abundance/expression	Name of the drug	Sensitive/resistant
KRAS	exon2 c.G35A p.G12D	15.14 %	Cetuximab/Panitumumab	Resistant (Level A)
			Regorafenib	Reduced sensitivity (Level A)
BRAF	No pathogenic mutations detected	-	Bevacizumab + Chemotherapy	Sensitive (Level A)
NRAS	No pathogenic mutations detected	-	Onvansertib + Bevacizumab + Chemotherapy	Sensitive (Level B)
			BGB-283	Sensitive (Level C)
TP53	Exon5 c.G527A p.C176Y	20.18 %	AZD1775(+Chemotherapy)/Pazopanib + Vorinostat	Sensitive (Level C)

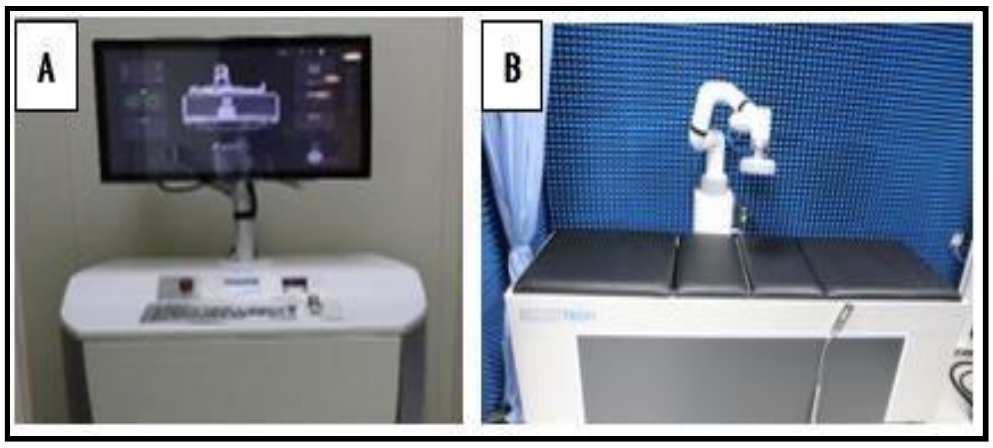


Figure 1: China's first self-developed intelligent dynamic energy-concentrating targeted hyperthermia system (A 4D treatment plan can be developed, and the intelligent robot can be used for spatial positioning to perform hyperthermia with circular, linear, and point-shaped trajectories)

A: treatment platform, B: treatment planning platform.

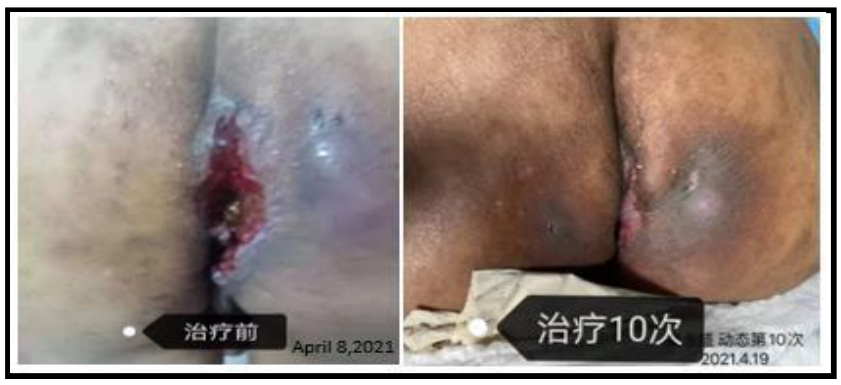


Figure 2: Comparison of lesions before and after hyperthermia.

The left image shows the lesions with ulceration and swelling before treatment. The right image shows a significantly reduced and partially healed ulceration and the growth of fresh granulation tissue after treatment.

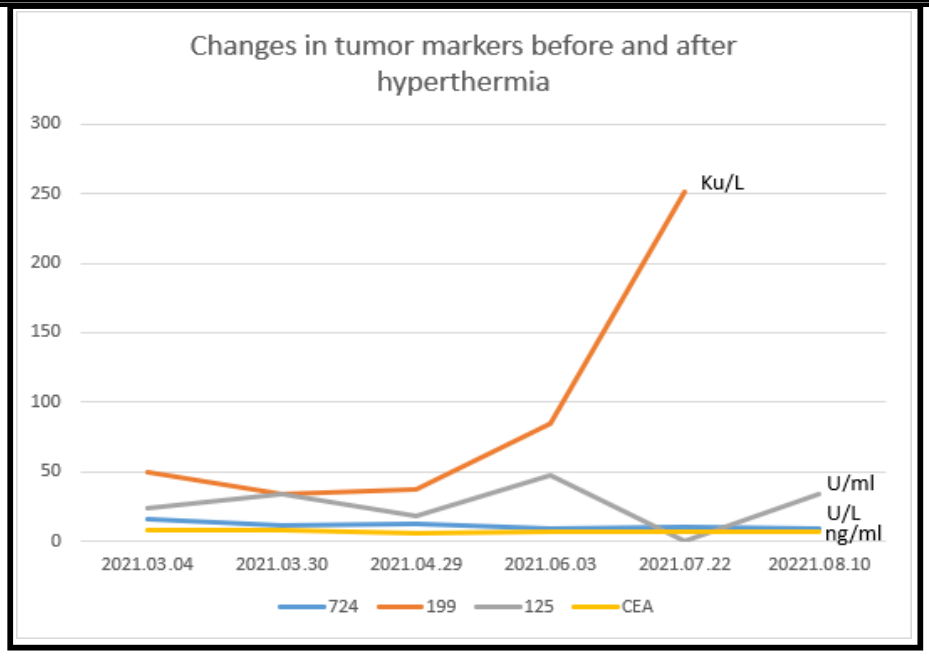


Figure 3: Changes in tumor markers before and after hyperthermia

The tumor markers CA724, CA125, and CEA decreased after hyperthermia combined with chemotherapy, and CA199 decreased at the beginning of hyperthermia but increased at a later stage.

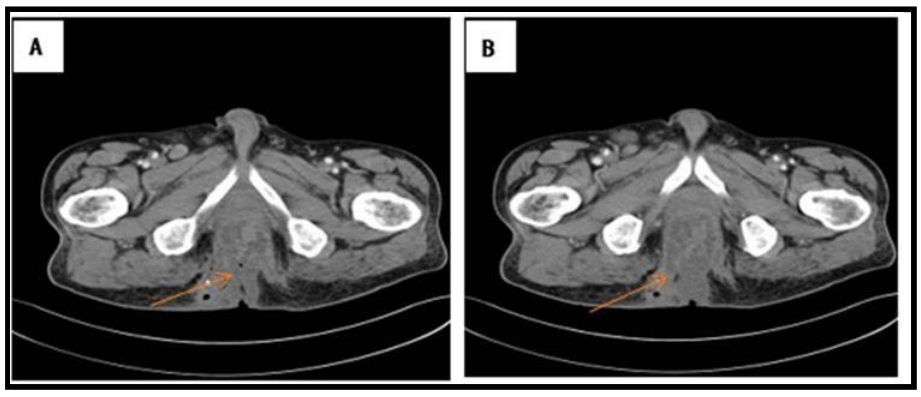
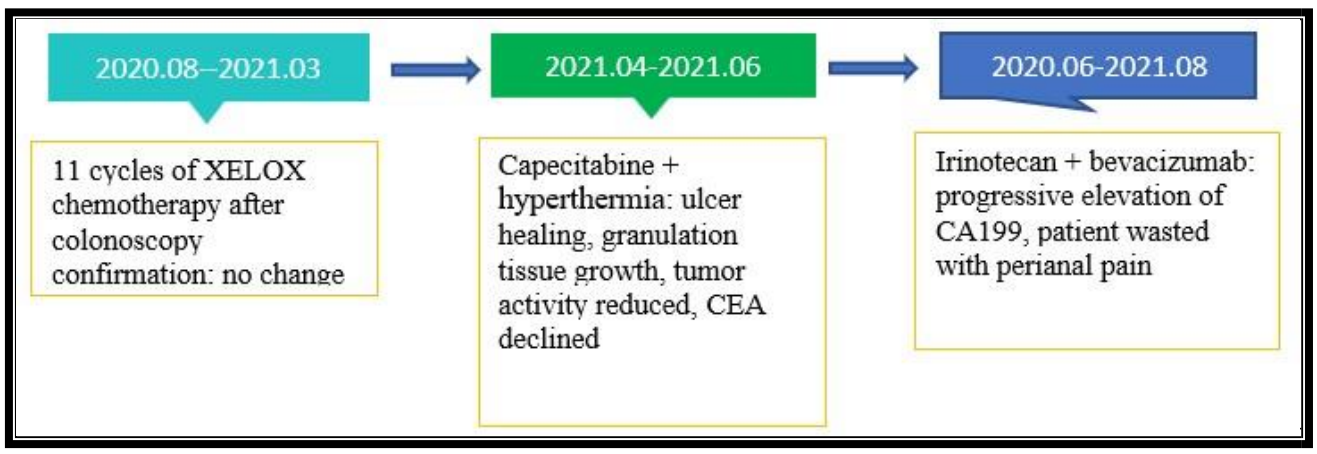


Figure 4: Changes in tumor activity before and after hyperthermia

A: before the hyperthermia. Rectum has a 10.1*4.3cm mixed density shadow.

B: after the hyperthermia. Rectum has a 10.3*4.6cm mixed density shadow. Decreased tumor CT values and cystic tumor changes can be seen after hyperthermia, suggesting tumor activity has decreased.

Treatment history：



2. Discussion

Worldwide, colorectal cancer (CRC) incidence has been on the rise. It is currently the third most common cancer in men (746,000 cases, 10.0 % of the total) and the second in women (614,000 cases, 9.2 % of the total) **[8]**. Approximately 60 % of patients are diagnosed at an advanced stage, chemotherapy and radiation therapy are included as treatment methods in many guidelines **[9]**, and chemotherapy or sequential therapy results in continuous improvements in local tumor control and cure rates **[10]**, becoming the gold standard for colorectal cancer treatment. However, the toxicity of the treatment, including bone marrow suppression, vomiting, and nausea, hinders effects, leading to certain limitations in clinical use **[11]**. Therefore, identifying a new model of treatment is of great clinical significance. Hyperthermia is an emerging painless, non-invasive, green, and accurate cancer treatment method after the traditional treatment method, which has been widely used in adjuvant therapy and palliative treatment of various tumors and has received wide attention from many clinicians and researchers. The basic principle is to use multiple physical energy to produce thermal effects in human tissues such that the local temperature of tumor cells is increased to the effective treatment temperature and maintained for a certain period. The difference in temperature tolerance between normal cells and

tumor cells is used to kill tumor cells and avoid destroying normal tissues. The applicability of hyperthermia in the treatment of tumors is based on the cytotoxic effect of high temperatures on tumor cells: temperatures from 41 °C to 44 °C are non-toxic to normal cells but toxic to tumor cells **[12]**. Because tumor cells are highly heated sensitive, when heated at temperatures 3 to 7 °C higher than normal cells, a suitable temperature can kill tumor cells without damaging neighbouring normal cells **[13]**.

The vascular composition of solid tumors is complex, including hypoxia and low pH zones, which are not present in normal tissues that are not disturbed. These environmental factors render tumor cells more sensitive to hyperthermia. The effect of hyperthermia depends on the temperature and the duration of treatment. Most normal tissues are not damaged when treated for 1 h at temperatures up to 44 °C. In this case, each hyperthermia session lasted 40 minutes, and the patient had no adverse reactions. Recent clinical trial results showed that **[14]** hyperthermia effectively treats a wide range of cancers as an adjunct to radiation or chemotherapy. In recent years, scholars studying hyperthermia in oncology domestic and international have conducted extensive academic research and clinical trials, showing that hyperthermia can significantly increase the local control rate of conventional treatment methods on tumors and improve long-term survival having an incomparable effect on the unique impact of other treatment methods **[15]**—the combination of hyperthermia with chemotherapy results in the overall alleviation of drug cytotoxicity. An artificial increase in tissue temperature can increase the fluidity of the phospholipid bilayer in tumor cells, thereby promoting drug permeability. In this case, a repeated C.T. scan of the lesion after hyperthermia combined with chemotherapy showed a decrease in the C.T. value of the lesion, suggesting a reduction in tumor activity and a progressive reduction in tumor marker levels.

Hyperthermia (> 41°C) increases tumor cell killing by enhancing the induction of DNA by chemotherapy and immune complexes, resulting in tumor cell cycle arrest **[16]**. It can not only improve the antitumor effect of chemotherapy without increasing side effects but also reduce the dose of chemotherapy drugs, thereby reducing the adverse reactions of chemotherapy and achieving the clinical effect of "efficiency and toxicity reduction." **[17]** Li et al. found that the combination of hyperthermia and chemotherapy could improve cancer patients' long-term survival and short-term efficacy. For patients with recurrent and metastatic rectal cancer, chemotherapy combined with hyperthermia can achieve better palliative treatment. **[18]** Zhang et al. studied the impact of deep term chemotherapy on the survival and prognosis-related factors of patients with recurrent metastatic colorectal cancer. They found that the median survival time of the term chemotherapy group was significantly better than that of the chemotherapy group (23 months vs. 18 months, $P < 0.05$), suggesting that chemotherapy combined with hyperthermia can improve the overall survival of patients. We investigated the efficacy of local deep hyperthermia combined with chemotherapy in treating locally advanced rectal cancer in this case. The results also showed that hyperthermia combined with chemotherapy improved the quality of life and survival of patients with locally advanced rectal cancer. The patient with a giant ulcer could not undergo surgery and radiotherapy. Genetic testing showed no mutated genes and no indications for targeted therapy. The choice of hyperthermia was critical. The compliance and tolerance of patients to hyperthermia combined with chemotherapy with capecitabine monotherapy is good, reserving physical energy and bone marrow function for subsequent possible two-drug combination chemotherapy.

With a further understanding of the biological behavior of tumor cells and the continuous improvement of treatment techniques, the comprehensive therapy of hyperthermia combined with chemotherapy is gradually being studied and practiced, and an increasing number of oncologists are slowly accepting the therapeutic effect. This treatment model has been utilized to treat ovarian cancer, gastrointestinal tumors, and other types of tumors. **[19]**

The characteristics of this case were the advanced stage of rectal cancer with giant perineal ulcers. The ulcers gradually decreased after hyperthermia combined with chemotherapy, and local control was adequate. These results suggest that in patients with advanced rectal or anal canal cancer when local symptoms are poorly controlled, comprehensive antitumor treatments such as local deep hyperthermia combined with chemotherapy can have significant survival benefits. A well-designed combination regimen can achieve a degree of survival gain and reduced toxicity, and local symptoms can be relieved **[20]**, which can improve patients' quality of life and tumor control rate. This is rarely reported in clinical practice. This case provides a new treatment idea for clinical practice. Hyperthermia combined with chemotherapy for advanced rectal cancer can benefit patients clinically. This treatment regimen should be used as soon as possible to achieve better treatment effects, alleviate symptoms of discomfort, improve quality of life, and extend survival time.

Core tips:

Rectal cancer is a common malignant tumor of the digestive tract and has a low early diagnosis rate. The clinical symptoms are atypical, the 5-year survival rate after surgery alone is less than 70 %, and the patient's quality of life is low. The efficacy of conventional postoperative adjuvant radiotherapy for local symptom control is unsatisfactory. Local deep hyperthermia combined with chemotherapy can reduce the local recurrence rate and improve survival and quality of life.

Disclosure statement: The authors do not have any possible conflicts of interest.

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