Radiosensitization treatment using hydrogen peroxide for inoperable rectal cancer

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Abstract. The treatment outcomes of patients with unresectable rectal cancer are complex, and concurrent chemoradiation therapy is the main treatment option. Radiosensitizers can enhance the effect of localized intratumoral hypoxia, contributing to local control and symptomatic relief. The present study evaluated the feasibility and safety of radiosensitization using hydrogen peroxide combined with radiation therapy (RT) in patients with unresectable rectal cancer. A total of 13 patients with rectal cancer were recruited in the present study. Radiosensitization was performed twice weekly in combination with RT. Gauze soaked in 3% hydrogen peroxide solution was inserted into the anus, ensuring firm contact with the lesion. In total, 45-65 Gy was delivered in 25-33 fractions to the whole pelvis from four directions using 10 MV X-rays 5 days per week. Acute and late adverse events were evaluated 1 and 6 months after the completion of RT. Treatment was well tolerated, with no acute grade 3 or worse events noted, and no patient developed rectal fistula, necrosis, obstruction, perforation, stenosis, ulcer or retroperitoneal hemorrhage. No notable late adverse events, beyond 6 months, were observed at the end of the analysis. All patients experienced pain relief, hemostatic effects and tumor shrinkage. Therefore, the use of a hydrogen peroxide solution-soaked gauze in the rectum may be a promising option for patients with inoperable rectal tumors. The limitations of the present study are that the patient population was small and the observation time was relatively short. This study was retrospectively registered with the University Hospital Medical Information Network Center (trial registration no. R000061902) on April 21, 2024.

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Abbreviations: RT, radiation therapy; CT, computed tomography; KORTUC, Kochi oxydol-radiation therapy for unresectable carcinomas; CTCAE, common terminology criteria for adverse events; VRS, verbal rating scale

Key words: radiosensitization, hydrogen peroxide, rectal cancer, unresectable, chemoradiotherapy

Introduction

Rectal cancer is common in both sexes, with 52,000 new cases reported in Japan in 2018 (1). Rectal cancer is more common in middle- and older-aged adults. Moreover, the risk is highest for individuals aged ≥50 years, and the incidence increases with advancing age (2). Although there are sex differences, recent trends suggest that the gap between females and males is narrowing. Risk factors for rectal cancer include a family history of the disease, genetic factors, history of inflammatory bowel disease, smoking, obesity, and dietary habits (3). This risk is particularly elevated in patients with a family history or involvement of genetic factors. The treatment methods for rectal cancer are advancing annually and involve a combination of surgery, radiation therapy, and chemotherapy, which have improved patient survival rates (4,5).

The treatment of rectal cancer varies depending on the cancer stage (extent of the disease) and the patient's overall health condition. In the early stages of rectal cancer, standard treatment typically involves surgery (6). The type of surgery, such as low anterior or abdominoperineal resection, varies depending on the location of the disease. Radiotherapy (RT) can be administered before or after surgery to shrink tumors. In cases where surgery is not feasible, RT can also be a primary treatment option. Chemotherapy is sometimes administered before or after surgery or in combination with RT. This approach aims to eliminate the cancer cells and prevent recurrence. Adjuvant RT, with or without chemotherapy, is recommended to improve the outcomes of patients with rectal cancer (7-9).

Treatment outcomes for patients with unresectable rectal cancer are complex and dependent on individual factors. The main treatment options for patients who cannot undergo surgery for rectal cancer include concurrent chemoradiotherapy (CCRT), RT, and chemotherapy (10). The purpose of these treatments is sometimes to cure cancer by eliminating cancer cells; however, in most cases, the treatments are palliative, aiming to alleviate symptoms and improve the quality of life of the patient.

The presence of hypoxic cells causes a decrease in the therapeutic effects of radiotherapy for various tumor sizes.

Moreover, most cancer types contain numerous hypoxic cells and large amounts of antioxidative enzymes (11). Ionizing radiation causes DNA damage by generating free radicals (12), which lead to cell death; however, under hypoxic conditions, DNA free radicals can return to their original form due to low oxygen levels, thus compromising radiation-induced DNA damage in hypoxic tumor cells (2). Therefore, tumor hypoxia is a major constraint in RT and chemotherapy (13). Several strategies for enhancing the effects of radiation have been proposed and evaluated in clinical studies (14-16). A new radiosensitizer, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas (KORTUC) II, has been developed, and its efficacy in tumors irradiated in the presence of hydrogen peroxide has been evaluated (14). Aoyama *et al* revealed the efficacy of KORTUC II in the treatment of recurrent breast cancer, stage IV primary breast cancer, and primary breast cancer without surgery (15). Moreover, Nishioka *et al* assessed the safety of KORTUC for unresectable cancers treated with intraoperative RT in combination with external beam RT and systemic chemotherapy and showed that it was both safe and effective (16).

Radiosensitizers can be used to enhance the effects of localized intratumoral hypoxia. Therefore, the local radiation-sensitizing effect of hydrogen peroxide may contribute to achieving local control and providing symptom relief in patients with unresectable rectal cancer. This study evaluated the feasibility and safety of radiosensitization using hydrogen peroxide combined with RT in patients with unresectable rectal cancer.

Materials and methods

Study design. A single-institution phase I clinical trial of hydrogen peroxide radiosensitization was performed using hydrogen peroxide for radiation in patients with unresectable rectal cancer. Patients with unresectable rectal cancer, who refused to undergo resection for rectal cancer, or who had recurrent rectal cancer were included in this study. Tumors were histologically proven to be locally advanced rectal cancers. Patients were required to be 20 years or older, with a performance status of 0 or 1. There was no restriction regarding previous treatments including previous use of radiotherapy on the pelvis. The use of concomitant chemotherapy was not restricted. Moreover, there was no restriction regarding the intent of treatment. Therefore patients were treated with radical radiotherapy and also palliative radiotherapy. The primary endpoints were the safety and tolerability of radiosensitization, regarding safety the evaluating method written at the end of the material and method section was used and regarding tolerability, we recorded how many patients we had to discontinue the radiosensitization because of side effects or patient's refusal. The secondary endpoints were the response of the tumor to radiosensitization and the amount of symptom palliation (pain or melena). Regarding this, the evaluation method written at the end of the material and method section was used. The trial was approved by the review board of Juntendo University Urayasu Hospital. Written informed consent was obtained from all patients.

Treatment planning. Treatment planning was performed using a Pinnacle 3 treatment planning system (Philips Medical Systems, Inc.) with computed tomography (CT) imaging (Canon, Aquilion Lightning, Japan). The patient began treatment 2 working days after CT imaging. The clinical target volume was created by contouring the tumor and regional lymph nodes. The planning target volume incorporated an additional 5 mm set-up margin to the clinical target volume.

Radiosensitization. Radiosensitization treatment was performed twice a week to avoid severe adverse events because the mucous membranes are more sensitive to X-rays than the skin. Therefore, hydrogen peroxide was used twice a week in combination with RT. Because the anticipated potential risk of this radiosensitization was adverse effects on the mucosal tissue surrounding the tumor, we referred to the method of radiosensitization used in patient with cervical cancer, which was reported in the literature (17). Here 3% hydrogen peroxide solution-soaked gauze was inserted into the vagina during RT twice a week. Because this study showed no severe acute and adverse effects, this method was employed. Immediately before RT, gauze soaked in 3% hydrogen peroxide solution was inserted into the anus, ensuring firm contact with the lesion. First a careful rectal palpation was performed to investigate the place and approximate diameter of the rectal stricture. Furthermore, because the radiosensitization can cause sever mucositis, the level of pain was checked by careful rectal palpation. Then using the anoscope, a visual inspection was performed to visually rule out severe mucositis. Through these investigations, we decided if the radiosensitization could be safely continued or should be discontinued. If the decision to continue the radiosensitization were made alongside the anoscope. the gauze would be inserted into the rectal stricture. The gauze was intended to be inserted only for the duration of the treatment (~10 min) and was removed immediately following RT. All procedures were performed by a dedicated radiation oncologist. The RT dose was 45-60 Gy over 25-33 fractions delivered to the whole pelvis from four directions using 10 MV X-rays from a linear accelerator (Elekta Synergy Platform; Elekta Instrument AB) 5 days per week. Acute and late adverse events were evaluated 1 and 6 months after the completion of RT. The evaluation was limited to the rectal mucosa and perianal area to evaluate only the side effects of the radiosensitization. To assess toxic effects and melena, adverse events were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE ver. 4.0) (18). The tumor response to radiosensitization was evaluated using the response evaluation criteria in solid tumors (19). The measurement of tumor size was performed on an axial or sagittal reconstructed image in the MRI (T2-weighted image) and the maximum diameter of the tumor was employed. Pain was assessed for symptom relief using a verbal rating scale (VRS). The VRS comprises a set of adjectives that characterize varying degrees of pain intensity: VRS0 indicates no pain, VRS1 mild pain, VRS2 moderate pain, VRS3 severe pain, and VRS4 extremely intense pain, thereby gauging the intensity of pain. To evaluate the amount of analgesics required, a scale modified from the World Health Organization pain relief ladder was used (Table I) (20).

Results

This study was conducted at our institution between September 2014 and November 2021. After ensuring full understanding

Table I. Analgesic score describing the amount of analgesics used.

Score	Score description
0	No analgesic
1	Non-opioid analgesic (e.g., NSAIDs or acetaminophen)
2	Weak opioids (e.g., codeine or tramadol)
3	Strong opioids ≤40 mg oral morphine equivalent per day
4	Strong opioids >40-80 mg oral morphine equivalent per day
5	Strong opioids >80-120 mg oral morphine equivalent per day
6	Strong opioids >120-180 mg oral morphine equivalent per day
7	Strong opioids >180 mg oral morphine equivalent per day

NSAIDs, non-steroidal anti-inflammatory drugs.

Table II. Patient (n=13) and tumor characteristics.

Characteristic	Number of patients
Median age, years (range)	80 (54-94)
Sex	
Male	7
Female	6
New case/recurrence	
New	6
Recurrence	7
Pathology	
Adenocarcinoma	12
Squamous cell carcinoma	1
Stage	
I	3
II	1
III	8
IV	1
Performance status	
0	8
1	5
Reason of surgery refusal	
Local recurrence after surgery	3
Local recurrence after chemoradiotherapy	1
Not a candidate for surgery due to comorbidities	7
Patient refusal of surgery	2

Table III. Acute adverse effects assessed according to Common Terminology Criteria for Adverse Events (version 4.0).

	Grade		
Adverse event	0	1	2
Proctitis	5 (38.5%)	0	8 (61.5%)
Rectal hemorrhage	10 (76.9%)	2 (15.4%)	1 (7.7%)
Rectal mucositis	12 (92.3%)	1 (7.7%)	0
Rectal pain	11 (84.6%)	2 (15.4%)	0

and obtaining written informed consent, the participants were enrolled. Thirteen patients met the inclusion criteria and agreed to participate. The patient characteristics are summarized in Table II. Out of the patients, 7 underwent chemoradiotherapy with tegafur gimeracil oteracil potassium and all the other underwent radiotherapy alone.

The median follow-up period was 14 (range 7-54) months. A summary of acute adverse events is shown in Table III. None of the patients had a rectal fistula, necrosis, obstruction, perforation, stenosis, ulcer, or retroperitoneal hemorrhage. The treatment was well tolerated, with no acute grade 3 or worse complications due to gauze insertion. All patients whose follow-up period exceeded 6 months were evaluated for late adverse events. Four patients were excluded because their follow-up periods were too short. No notable late adverse events were observed at the end of the study.

Before treatment, five patients experienced pain around the rectum, and three patients used analgesics. In all cases, pain relief to VRS0 was observed. In two patients, analgesics were discontinued. However, in three patients, the pain recurred after a median of 7 (range 3-14) months after the completion of radiotherapy. Rectal bleeding was observed in eight patients before treatment. In all patients, bleeding stopped, but in three of them, rebleeding was observed at a median of 7 (range 4-20) months after the completion of RT. In all patients, magnetic resonance or CT images before and after irradiation were available; therefore, the tumor size before and after radiotherapy could be compared. Tumor size was measured 1 month before radiation treatment and 3 months after treatment initiation. In five patients, tumor size reduction was observed compared with the size before treatment. The individual patient outcomes are summarized in Table IV.

Discussion

The radiosensitization treatment KORTUC was combined with external RT for unresectable tumors and recurrent breast

Table IV. Summary of all patient outcomes.

Patient	Age, years	Sex	Total dose, Gy	Follow-up period, months	Combined chemotherapy	Maximum diameter, mm	
						Before	After
1	82	Male	59.4	20	TS1	37	16
2	88	Female	59.4	12	None	35	30
3	94	Male	59	6	None	38	36
4	84	Female	59.4	5	TS1	27	22
5	82	Female	59.4	10	None	44	30
6	70	Male	46.8	51	None	41	22
7	64	Male	60	5	TS1	42	30
8	54	Female	45	19	None	27	18
9	85	Male	59.4	10	TS1	33	27
10	57	Male	45	26	TS1	35	28
11	60	Male	45	19	TS1	33	25
12	57	Female	59.4	49	TS1	40	30
13	80	Female	59.4	13	None	69	24

TS1, tegafur gimeracil oteracil potassium.

cancer (21,22). Previous clinical trials have demonstrated the efficacy of RT combined with KORTUC (23-25).

Miyatake *et al* (21) evaluated the therapeutic outcomes of locally advanced breast cancer with systemic chemotherapy without surgical intervention using a 6 ml radiosensitizer injection.

In total 49.5 Gy was delivered (hypofractionated RT at 2.75 Gy per fraction). Seventeen patients were included in the study. The therapy was well tolerated, all patients achieved a complete response to their primary breast tumors, and no findings of local recurrence were observed during the follow-up period. Nishioka *et al* (16) reported the safety and efficacy of a radiosensitizer injection technique for stage IVa locally advanced unresectable pancreatic cancer using ultrasonic guidance for interoperative RT (the total dose of 25 Gy was delivered in 1 fraction). Twelve patients were included. The 1- and 2-year overall survival rates were 75 and 25%, respectively, and the median survival was 16 months. The authors concluded that the treatment was well tolerated and showed no serious complications.

Aoyama *et al* (22) evaluated the safety and efficacy of KORTUC II in patients with stage I primary breast cancer. KORTUC II is a solution comprising of 0.83% sodium hyaluronate and 0.5% hydrogen peroxide. Hyaluronate was added to maintain the agent in the injected tumor for a longer time. The 15 patients were injected with 3 ml of KORTUC II agent into the tumor concomitant with RT twice a week. All patients exhibited complete response; the 5-year overall survival rate was 100%. The authors concluded that KORTUC II was an effective radiosensitizer with satisfactory treatment outcomes.

A previous study from our institution showed the feasibility and safety of radiosensitization using hydrogen peroxide for patients with cervical cancer who are ineligible for brachytherapy (17). Briefly, 18 patients received treatment comprising a 3% hydrogen peroxide solution-soaked gauze inserted into the vagina during RT twice a week. In tota, l45 Gy was delivered in 25 fractions to the whole pelvis, with an additional 10 Gy boost to the metastatic lymph nodes. The two-year overall survival rates of the 17 patients were 90% in stage I/II and 86% in stage III/IV (one patient with noninvasive cancer was excluded from the survival analysis). The adverse events were well tolerated with no severe acute or late adverse events.

Neoadjuvant CCRT is recommended for rectal adenocarcinoma, and surgical removal of the tumor and draining lymph node basins is used to reduce local recurrence rates. RT plays an integral role as it aids in downsizing or downstaging large tumors in the neoadjuvant setting.

Most of the patients in our study were patients who could not undergo surgery because of comorbidity and the second were local recurrent patients. Just for a reference we search the literature for radiotherapy of patients with locally recurrent rectal cancer. There were several successful reports of radiotherapy for patients with locally recurrent disease. Ito *et al* (26) reported the retrospective analysis of 30 patients with locally recurrent rectal cancer who underwent RT at their institution. Out of them, 17 received CCRT and 13 received RT alone. A median total dose of RT was 50 Gy. Grade 3 acute lower bowel toxicity was observed in 7% and grade 4 ileus was observed in 13% which occurred 2-11 months after completion of radiotherapy. Pain relief was observed in 90% of patients. Guren *et al* (27) reported a systematic review of seven prospective or retrospective studies, which presented results of 375 patients. CCRT was hyperfractionated (1.2-1.5 Gy twice-daily) or 1.8 Gy once-daily and the median total dose was 30-40 Gy. Grade 3 to 4 acute gastrointestinal toxicity was reported in 9-19% and late gastrointestinal toxicity was reported in 17%. Complete pain relief was observed in 47-94% of patients, and regarding the effect against rectal bleeding, two studies reported it, and both showed total relief. Lee *et al* (28) reported a meta-analysis of 17 studies involving 744 patients.

Conventional daily fractionation scheme with 1.8-2 Gy per day was used in 29.4, and 35.3% used twice daily fractions of 1.2-1.5 Gy. Pooled late grade 3 or worse acute toxicity was 11.4% and for late toxicity it was 25.2%. The pooled symptomatic palliation rate was 75.2%.

This prospective study analyzed the feasibility and safety of radiosensitization treatment using hydrogen peroxide in patients with rectal cancer who could not undergo surgery. No notable late adverse events grade 3 or worse were observed, and all patients completed the protocol. All patients experienced pain relief, hemostatic effects, and tumor shrinkage. These data were safe and the effect of symptomatic palliation was comparable to the data in the literature. However, regarding acute and late toxicity, our study was lower compared to the studies in the literature. Based on these results, radiosensitization with hydrogen peroxide combined with CCRT can be safely performed for the treatment of inoperable rectal cancer. In addition, because all patients showed symptom relief, radiosensitization may have contributed to the improved outcomes. This treatment could be a promising option for patients with inoperable rectal tumors.

This study has some limitations. First, the number of patients was small, and the observation time was relatively short. Second, because RT alone can relieve symptoms caused by cancer in many cases, the excellent treatment results shown in our study may have been obtained without radiosensitization. Therefore, we believe that our results must be interpreted with caution regarding the effectiveness of radiosensitization.

In conclusion, radiosensitization with hydrogen peroxide is feasible and can be achieved without the severe complications associated with palliative RT for inoperable rectal cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AS obtained the data, and conceptualized and designed the study. Both authors analyzed and interpreted the data, and KU drafted the manuscript. Both authors confirmed the authenticity of all the raw data. Both authors critically revised the manuscript for important intellectual content and agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. Both authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Juntendo University Urayasu Hospital (approval no. 2013-025). Written informed consent was obtained from all patients enrolled in this study.

Patient consent for publication

Written informed consent for publication was obtained from all patients enrolled in this study.

Competing interests

The authors declare that they have no competing interests.

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