The effect of mistletoe extract on tumor response in neoadjuvant chemoradiotherapy for rectal cancer

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Research

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Abstract

Background

Mistletoe extract, which is usually used as a complementary agent for cancer patients, provides an anticancer effect on various malignancies. The present study aimed to evaluate the effect of mistletoe extract (Abnoba Viscum Q®) on tumor responses in neoadjuvant chemoradiotherapy for locally advanced rectal cancer.

Methods

The rectal cancer patients who underwent neoadjuvant chemoradiotherapy were analyzed from Jan 2018 to Jul 2020. In the mistletoe group (MG), the patients were administered Abnoba Viscum Q® subcutaneously during chemoradiotherapy, and it was maintained just before surgery. Patients' demographics, clinical outcomes, and histopathological outcomes were compared between chemoradiation with the MG and nonmistletoe group (NMG).

Results

A total of 52 patients were included. There were MG of 15 patients and NMG of 37 patients. Baseline demographics were statistically similar between the two groups except the CA19-9 and tumor location levels from anal verge. There was no difference in the clinical stage for both groups. We also observed better tumor response in MG in terms of TRG, T stage, and overall TNM stage. Tumor response was significantly better in MG comparing NMG in terms of pathologic complete response rate (53.3% vs 21.6%, p = 0.044), good responder of tumor regression grade (66.7% vs 32.4%, p = 0.024), T downstaging (86.7% vs 43.2%, p = 0.004), and overall downstaging (86.7% vs 56.8%, p = 0.040). The toxicities during NCRT in both groups were minimal.

Conclusion

MG treated with chemoradiation combined with mistletoe extract showed better outcomes than NMG in terms of tumor responses. This diversity in treatment may elevate the method to hope for better oncologic outcomes. Prospective and randomized studies with long-term follow-up are warranted to confirm and extend this study.

Introduction

Colorectal cancer is one of the most common solid tumors with the third highest incidence and the second-highest mortality rate among malignancies worldwide [1]. The standard treatment for patients with locally advanced rectal cancer is neoadjuvant chemoradiotherapy (NCRT) before radical surgery to reduce locoregional recurrence and toxicity of chemoradiation [2, 3]. Tumor down-staging and pCR after NCRT for rectal cancer are associated with good survival outcomes compared to non-response to NCRT [4–8].

Although NCRT has been associated with reducing the locoregional recurrence of rectal cancer, locoregional recurrence causes poor oncologic outcomes to the patient. Therefore, it is essential to enhance tumor response

to achieve good oncological results in patients with rectal cancer treated with NCRT. More toxic chemoagents and biologics have been tried to add to conventional NCRT. Oxaliplatin or target agents have been added to NCRT for patients with advanced rectal cancer. Unfortunately, they increase toxicities without better tumor response [9–12]. We need a new regimen with little toxicity and good compliance for rectal cancer patients to raise the complete remission rate.

Mistletoe (scientific name: Viscum album) is a semi-parasitic plant in the order Santalales. The extracts from European mistletoe are widely used in complementary and alternative agents to treat patients with various malignancies, including colorectum, lung, oral, pancreas, and breast cancers. Their components, including viscotoxin and lectin, exhibit antitumor effect based on direct cytotoxicity and the increase of the cell mediated immunity [13, 14]. Mistletoe extracts showed safety and improved quality of life during chemotherapy in oncologic patients [15–17]. Although their antitumor effect and safety have been reported, so far, there is no clinical study regarding tumor regression after NCRT combined with mistletoe extract in rectal cancer. In the present study, we investigated the effect of mistletoe extract on tumor response in NCRT for patients with locally advanced rectal cancer.

Materials And Methods

Patients selection

A single-center retrospective observational study included the consecutive 52 patients with clinical stage □-□ rectal adenocarcinoma treated with long-course NCRT from January 2018 to July 2020 (for this period, mistletoe extract began to be used during NCRT) in Gil Medical Center: a tertiary-referral hospital. The patients with incomplete NCRT were excluded. The conditional searching of patient information was performed by the Clinical Research Data Warehouse (CRDW) system, and detailed data were collected from electronic medical records in Gil Medical Center.

The institutional review board approved the study through the ethics committee of our hospital (approval no. GFIRB2020-304).

Neoadjuvant chemoradiotherapy

All patients treated with long-course NCRT based on the National Comprehensive Cancer Network guidelines. Radiation that delivered 50.4 Gy in 28 fractions over five weeks in the pelvis was given to 53 patients. Dosing schedules for concurrent chemotherapy were capecitabine 825 mg/m2 per oral twice daily five days per week during pelvic radiotherapy, or 5-fluorouracil 400 mg/m2 intravenous bolus with leucovorin 20 mg/m2 intravenous bolus for four days during week 1 and 5 of NCRT.

Mistletoe extract

Abnoba Viscum Q® (ABNOBA GmbH, Pforzheim, Germany) was used for mistletoe extract. There was no criterion for selecting the patients to be treated with Abnoba Viscum Q®. The patients were administered it subcutaneously: firstly 0.02 mg/ample 3 times a week for 3 weeks, followed by 0.2 mg/ample 3 times a week for 3 weeks, and then 2 mg/ample 3 times a week for 3 weeks, and finally 20 mg/ample 3 times a week; the final 20mg dose was maintained just before surgery. The patients administered Abnoba Viscum Q® by

themselves after learning how to inject Abnoba from the medical staff, followed up in an outpatient clinic every 3 weeks, receiving the amples. The administration of Abnoba Viscum Q® was transiently halted if there were any local or systemic adverse events, such as severe urticarial, local swelling over 5 cm, or high fever over 38 °C.

Assessment parameters and statistical analysis

Patients demographics, clinical outcomes, and histopathological outcomes were compared between NCRT with mistletoe group (MG) and nonmistletoe group (NMG). Clinical TNM stage and mesorectal fascia (MRF) involvement were assessed by computed tomography and magnetic resonance image. Abdominoperineal CT and rectal MRI were performed twice before and after NCRT to evaluate the tumor and lymph node status. Tumor distance from anal verge (AV) was measured by magnetic resonance image. Tumor regression grade (TRG) was graded on a scale of 0 (complete response: no viable cancer cells) to 3 (poor or no response) according to American Joint Committee on Cancer (AJCC) classification [18]. Response to treatment were graded as good (AJCC grades 0 and 1) or poor responder (AJCC grades 2 and 3) 'T, N, and overall TNM downstaging' were defined as downstaging between baseline imaging results and pathologic stage after curative resection. Continuous variables were analyzed by Mann-Whitney test, and categorical variables were analyzed Chi-square test or Fischer's exact test. The significant differences of each variable between two groups were defined as p value less than 0.05. All statistical analyses were performed with IBM SPSS Statistics 23 for Windows (IBM SPSS Inc., Chicago, IL, USA).

Results

Baseline patient characteristics

A total of 52 patients were included. There were MG of 15 patients and NMG of 37 patients. The median age was 68 (range: 38–86) years, and the sex ratio was 35 men: 17 women. Baseline demographics were statistically similar between the two groups except CA19-9 and tumor distance from AV. CA 19 − 9 was higher in NMG (p = 0.01), and tumor distance from AV was longer in NMG (p = 0.008). MRF involvement presented 10 (66.7%) in MG, and 19 (51.4%) in NMG (p = 0.314). All of the patients in MG were clinically stage Ⅱ, while NMG showed 3 (8.1%) patients in stage Ⅱ and 34 (91.9%) patients in stage Ⅲ. There was no statistical difference in the clinical stage for both groups (p = 0.548). The details of baseline patient demographics are demonstrated in Table 1.

Table 1
Baseline patient demographics

Variables	MG (n = 15)	NMG (n = 37)	*p value*
Age (years)	68 (38 ~ 83)	67 (46 ~ 86)	0.864†
Sex			0.525¶
Male	9 (60.0)	26 (70.3)	
Female	6 (40.0)	11 (29.7)	
BMI (kg/m^2)	23.4 (20.8 ~ 28.3)	24.4 (15.1 ~ 31.5)	0.473†
ASA score			0.254¶
1	0	4 (10.8)	
2	15 (100)	30 (81.1)	
unknown	0	3 (8.1)	
Past history			
Diabetes	5 (33.3)	8 (21.6)	0.483¶
Cardiovascular disease	7 (46.7)	18 (48.6)	0.897¶
others	5 (33.3)	13 (35.1)	0.902¶
Baseline tumor markers			
CEA (ng/ml)	2.9 (0.5 ~ 43.7)	2.9 (0.6 ~ 44.9)	0.992†
CA 19 − 9 (U/ml)	4.2 (1.2 ~ 184.7)	12.1 (1.2 ~ 1222.8)	0.010† **
Tumor distance from AV (cm)	3.6 (0 ~ 10.0)	6.0 (2.0 ~ 10.0)	0.008† **
MRF involvement			0.314¶
yes	10 (66.7)	19 (51.4)	
no	5 (33.3)	18 (48.6)	
cT before NCRT			0.412¶
cT2	1 (6.7)	0	

Continuous variables are listed as median (range), and categorical variables are listed as n (%).

†Mann-Whitney test, ¶Chi-square test or Fisher's exact test, ** statistical significance ($p < 0.05$)

MG mistletoe group, NMG nonmistletoe group, BMI body mass index, ASA American Society of Anesthesiologist, AV anal verge, MRF mesorectal fascial, NCRT neoadjuvant chemoradiotherapy, AJCC American Joint Committee on Cancer

Variables	MG (n = 15)	NMG (n = 37)	*p value*
cT3	12 (80.0)	32 (86.5)	
cT4	2 (13.3)	5 (13.5)	
cN before NCRT			0.086¶
cN0	0	3 (8.1)	
cN1	7 (46.7)	6 (16.2)	
cN2	8 (53.3)	28 (75.7)	
Baseline clinical stage (AJCC 8th)			0.548¶
Stage 2	0	3 (8.1)	
Stage 3	15 (100)	34 (91.9)	
Continuous variables are listed as median (range), and categorical variables are listed as n (%).			
†Mann-Whitney test, ¶Chi-square test or Fisher's exact test, ** statistical significance ($p < 0.05$)			
MG mistletoe group, NMG nonmistletoe group, BMI body mass index, ASA American Society of Anesthesiologist, AV anal verge, MRF mesorectal fascial, NCRT neoadjuvant chemoradiotherapy, AJCC American Joint Committee on Cancer			

Perioperative outcomes

All patients received a total of 50.4 Gy of pelvic radiation. The median interval to surgery is 9 (range: 5.9–14.1) weeks after the completion of NCRT. The interval time in MG and NMG was 8,6 and 8.7 weeks, respectively, with no statistical difference ($p = 0.808$). All patients were treated with oral capecitabine in concurrent chemotherapy except one patient (5-fluorouracil/leucovorin). Surgery contained 11 low anterior resections, 34 ultra-low anterior resections, 2 abdominoperineal resections, 3 Hartmann's operations, and 2 transanal excisions. There was no statistical difference in perioperative clinical outcomes between both groups (Table 2).

Table 2
Short-term clinical outcomes of chemoradiation and surgery

Variables	MG (n = 15)	NMG (n = 37)	*p value*
Dose of radiation (Gy)	50.4	50.4	n/a
Concurrent chemotherapy			1.000¶
Capecitabine	15 (100)	36 (97.3)	
5-fluorouracil	0	1 (2.7)	
cT after NCRT			0.848¶
cT0	1 (6.7)	1 (2.7)	
cT2	6 (40.0)	12 (32.4)	
cT3	7 (46.7)	21 (56.8)	
cT4	1 (6.7)	3 (8.1)	
cN after NCRT			0.666¶
cN0	7 (46.7)	14 (37.8)	
cN1	6 (40.0)	14 (37.8)	
cN2	2 (13.3)	9 (24.3)	
Interval to surgery (weeks)	8.6 (6.1 ~ 12.9)	8.7 (5.9 ~ 14.1)	0.808†
Type of surgery			0.506¶
Low anterior resection	3 (20.0)	8 (21.6)	
Ultra-low anterior resection	10 (66.7)	24 (64.9)	
Abdominoperineal resection	1 (6.7)	1 (2.7)	
Hartmann operation	0	3 (8.1)	
Transanal excision	1 (6.7)	1 (2.7)	
Total operative time (hours)	3.0 (0.8 ~ 4.1)	3.0 (0.2 ~ 5.7)	0.428†
Estimated blood loss (mL)	20.0 (3.0 ~ 150.0)	30.0 (0 ~ 250.0)	0.385†
Intraoperative transfusion			n/a
Yes	0	0	

Continuous variables are listed as median (range), and categorical variables are listed as n (%).

†Mann-Whitney test, ¶Chi-square test or Fisher's exact test

MG mistletoe group, NMG nonmistletoe group, NCRT neoadjuvant chemoradiotherapy

Variables	MG (n = 15)	NMG (n = 37)	*p value*
No	15 (100)	37 (100)	
Length of hospital stay (days)	8 (4 ~ 37)	8 (5 ~ 51)	0.676†
Continuous variables are listed as median (range), and categorical variables are listed as n (%).			
†Mann-Whitney test, ¶Chi-square test or Fisher's exact test			
MG mistletoe group, NMG nonmistletoe group, NCRT neoadjuvant chemoradiotherapy			

Toxicity outcomes

Toxicity during NCRT was demonstrated in Table 3. According to Common Terminology Criteria for Adverse Events ver 3.0 (CTCAE), toxicity was stratified from grade 1 to grade 4. The most common toxicity for both groups was proctitis. There were 9 (60.0%) patients with grade 1 proctitis in the MG, and 10 (27.0%) patients with grade 1 proctitis in the NMG. Grade 2 neutropenia and grade 3 anemia were observed in the NMG, while no patients suffered from those adverse events in the MG. Pruritus with or without skin rash on the injection site was occurred in 3 (20.0%) patients in the MG, whereas there was no pruritus in the NMG ($p = 0.021$). All other adverse events, including nausea, vomiting, diarrhea, constipation, oral mucositis, and peripheral neuropathy, were grade 1, and there were no statistical differences between both groups.

Table 3
Toxicity outcomes

Toxicity	CTCAE								*p value*[¶]
	MG (n = 15)				NMG (n = 37)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
Neutropenia	0	0	0	0	0	1 (2.7)	0	0	1.000
Anemia	0	0	0	0	0	0	1 (2.7)	0	1.000
Thrombocytopenia	0	0	0	0	0	0	0	0	
Nausea	4 (26.7)	0	0	0	6 (16.2)	0	0	0	0.448
Vomiting	1 (6.7)	0	0	0	0	0	0	0	0.288
Diarrhea	2 (13.3)	0	0	0	5 (13.5)	0	0	0	1.000
Constipation	0	0	0	0	4 (2.8)	0	0	0	0.311
Proctitis	9 (60.0)	0	0	0	10 (27.0)	0	0	0	0.054
Oral mucositis	0	0	0	0	1 (2.7)	0	0	0	1.000
Peripheral neuropathy	1 (6.7)	0	0	0	0	0	0	0	0.288
Pruritus	3 (20.0)	0	0	0	0	0	0	0	0.021

Categorical variables are listed as n (%).

[¶]Chi-square test or Fisher's exact test

CTCAE Common Terminology Criteria for Adverse Events ver 3.0, MG mistletoe group, NMG nonmistletoe group

Evaluation of tumor responses

Estimations of pCR, downstaging, and TRG were assessed in histopathologic reports after curative surgery. Table 4 shows the histopathological outcomes after curative resection. There were no statistical differences in tumor size, histologic grade, ypN stage, distal resection margin, circumferential resection margin involvement, harvested lymph nodes, and perineural invasion between both groups. However, ypT stage presented the trend toward higher stage in NMG than MG ($p = 0.005$). Lymphovascular invasion was more frequently detected in NMG than MG (32.4% vs 13.3%, $p = 0.04$)

Table 4
Histopathological outcomes

Variables	MG (n = 15)	NMG (n = 37)	*p value*
Tumor size (cm)	2.5 (0 ~ 4.5)	3 (0 ~ 7.7)	0.293†
Histologic grade			0.151¶
well differentiated	0	1 (2.7)	
moderate differentiated	6 (40.0)	25 (67.6)	
poorly differentiated	1 (6.7)	2 (5.4)	
others	8 53.3)	9 (24.3)	
ypT after NCRT			0.005¶ **
ypT0	8 (53.3)	8 (21.6)	
ypT1	0	1 (2.7)	
ypT2	5 (33.3)	4 (10.8)	
ypT3	2 (13.3)	22 (59.5)	
ypT4	0	2 (5.4)	
ypN after NCRT			0.161¶
ypN0	13 (86.7)	21 (56.8)	
ypN1	2 (13.3)	12 (32.4)	
ypN2	0	4 (10.8)	
Distal resection margin (cm)	1.5 (0.2 ~ 6.0)	2.0 (0.1 ~ 5.0)	0.121†
Circumferential resection margin involvement			0.498¶
yes	1 (6.7)	1 (2.7)	
no	14 (93.3)	36 (97.3)	
Harvested lymph nodes	13 (1 ~ 18)	13 (1 ~ 35)	0.255†
Lymphovascular invasion			0.04¶ **
yes	2 (13.3)	16 (43.2)	

Continuous variables are listed as median (range), and categorical variables are listed as n (%).

†Mann-Whitney test, ¶Chi-square test or Fisher's exact test, ** statistical significance ($p < 0.05$)

MG mistletoe group, NMG nonmistletoe group, NCRT neoadjuvant chemoradiotherapy, yp pathological status after NCRT

Variables	MG (n = 15)	NMG (n = 37)	*p value*
no	13 (86.7)	21 (56.8)	
Perineural invasion			0.3¶
yes	2 (13.3)	12 (32.4)	
no	13 (86.7)	25 (67.6)	
Continuous variables are listed as median (range), and categorical variables are listed as n (%).			
†Mann-Whitney test, ¶Chi-square test or Fisher's exact test, ** statistical significance ($p < 0.05$)			
MG mistletoe group, NMG nonmistletoe group, NCRT neoadjuvant chemoradiotherapy, yp pathological status after NCRT			

Tumor responses were significantly better in MG comparing NMG in terms of pCR rate (53.3% vs 21.6%, p = 0.044), good responder of TRG (66.7% vs 32.4%, p = 0.024), T down staging (86.7% vs 43.2%, p = 0.004), and overall TNM down staging (86.7% vs 56.8%, p = 0.040). Otherwise, N downstaging showed no statistical difference between both groups (93.3% vs 78.4%, $p = 0.257$). Table 5 demonstrated the details of tumor responses.

Table 5
Tumor response between mistletoe group and nonmistletoe group

Variables	MG (n = 15)	NMG (n = 37)	*p value*
pCR			0.044¶ **
yes	8 (53.3)	8 (21.6)	
no	7 (46.7)	29 (78.4)	
TRG (AJCC)			0.024¶ **
good responder (0–1)	10 (66.7)	12 (32.4)	
poor responder (2–3)	5 (33.3)	25 (67.6)	
T downstaging			0.004¶ **
yes	13 (86.7)	16 (43.2)	
no	2 (13.3)	21 (56.8)	
N downstaging			0.257¶
yes	14 (93.3)	29 (78.4)	
no	1 (6.7)	8 (21.6)	
Overall TNM downstaging			0.040¶ **
yes	13 (86.7)	21 (56.8)	
no	2 (13.3)	16 (43.2)	
Categorical variables are listed as n (%).			
¶Chi-square test or Fisher's exact test, **statistical significance ($p < 0.05$)			
MG mistletoe group, NMG nonmistletoe group, pCR pathologic complete response, TRG tumor regression grade, AJCC American Joint Committee on Cancer			

Discussion

To our knowledge, this is the first study that analyzed the response of tumors after NCRT, comparing MG and NMG of patients with locally advanced rectal cancer. The current study represents that additional administration of mistletoe extract combined with NCRT shows promising results for tumor responses, including T-stage, lymphovascular invasion, TNM stage, TRG, and pCR. These results proposed that mistletoe extract may lead to more improved oncologic outcomes.

Rectal cancer, which is approximately one-third out of colorectal cancer, has relatively higher locoregional recurrence rates than colon cancer because mid-to-lower rectum has no serosa to protect tumor invasion through the muscle layer, and it is technically more demanding to obtain enough safety margin [19]. In addition,

it is technically challenging to achieve sufficient resection margin to prevent locoregional recurrence due to the close proximity to pelvic structures and organs.

Chemoradiotherapy for rectal cancer usually is needed locoregional therapy due to the relatively high risk of locoregional recurrence compared to colon cancer. Preoperative irradiation is more effective because tumor oxygenation is better with preoperative therapy than postoperative therapy [20]. NCRT improved locoregional control and associated with reduced toxicity compared to postoperative chemoradiotherapy [2, 21]. NCRT using 5-FU or capecitabine is usually used as standard therapy for locally advanced rectal cancer before radical surgery [22, 23]. NCRT of stage II or III of rectal cancer before surgery improves locoregional control and reduces the toxicity of chemoradiation [2, 24]. Despite these treatment efforts, the 5-year incidence of locoregional recurrence rates of rectal cancer is reported to range from 6 to 10.7% [2, 8, 25, 26]. Tumor downstaging and pCR after NCRT facilitate increased overall survival and disease-free survival, including locoregional therapy [4–8]. Therefore, it is crucial to get more tumor downstaging and pCR to achieve good oncological results in patients with rectal cancer treated with NCRT.

In terms of the period from the completion of NCRT to surgery, curative surgery is recommended within 5 ~ 12 weeks. Longer intervals (more than the classical 6 ~ 8 weeks) from completion of NCRT increase the rate of pCR by 6% in rectal cancer [27]. The interval over 8 weeks is associated with increased odds of pCR compared with an interval of 6 to 8weeks [28]. The median interval to surgery in current study was 8.6 weeks in MG and 8.7 weeks in NMG.

Mistletoe is a parasitic plant that parasite on trees. It was first introduced as a cancer treatment by Rudolf Steiner [29]. Cancerostatic protein components from Viscum album were identified later as the cytotoxic viscotoxins and mistletoe lectins [30]. The mistletoe extract induces apoptosis and cytotoxicity to cancer [31]. It also stimulates immunocompetent cells to promote immunomodulation by mistletoe lectin as beta-galactoside-specific lectin [32]. The most important pharmacological components of mistletoe extract are lectins and viscotoxins, which exhibited antitumoral and immunomodulating effects. Mistletoe extract had been considered as a proven old medicine for various cancer patients. However, so far mistletoe therapy to patients with cancer has been controversial in terms of quality of life and oncologic outcomes in the literature [33–36].

Abnoba Viscum Q® showed the radioprotective effect, and it was similar to the effect of amifostine that was approved as a clinical radioprotectant [37]. Viscotoxin in mistletoe extract had potential antioxidant activity [38]. Mistletoe extract combined with chemotherapy and/or radiotherapy was used for the stage I-III colorectal cancer, showing reduced adverse reaction after adjuvant therapy and better oncologic outcomes in terms of disease-free survival [39]. We adopted Abnoba Viscum Q®, which was expected as the dual effects, radioprotectivity and tumor regression, in the patients with locally advanced rectal cancer.

Tumor regression after conventional NCRT appears in the majority of patients, and approximately 12–38% of patients can achieve pathologic complete response (pCR) [40]. To enhance pathologic tumor response and improve locoregional control, more toxic chemoagents and biologics, including oxaliplatin or target agents, have been tried to add to conventional NCRT to increase pCR and improve oncologic outcomes including reduced recurrence in patients with rectal cancer. However, oxaliplatin as a radiation sensitizer did not improve clinical outcomes, including pathologic complete response, and patients' survival, while it increased

chemotoxicity [9, 10, 41–43]. Clinical studies including target agents such as cetuximab, panitumumab, and bevacizumab in NCRT for advanced rectal cancer did not increase pCR, but instead increased significant toxicities [11, 12, 44, 45]. It is needed a new agent to enhance tumor regression for the patient with rectal cancer with less toxicity. Recently, metformin was applied to NCRT together in rectal cancer, and a good tumor response rate and cancer-specific survival as well as lower risk of cancer recurrence were reported [46]. We applied mistletoe extract approved by the Korean Food and Drug Administration (KFDA) as an anti-malignant drug to NCRT for advanced rectal cancer to enhance tumor response. The pCR rates in the mistletoe and NMG were 53.3% and 21.6%, respectively, showing almost twice the effect, and statistically significant. T downstaging and overall downstaging in MG and NMG show 86.7% vs 43.2% and 86.7% vs 56.8%, respectively with significant differences. Lymphovascular invasion was less frequently detected in MG than NMG (13.3% vs 32.4% vs $p = 0.04$). Although this study is retrospective and not randomized, the results are very encouraging compared to previous studies [9, 10, 27, 40–42]. We expect good oncological results in the future by using additional mistletoe extract for NCRT in rectal cancer with these pathological results.

Patients receiving NCRT with more toxic chemoagent, including oxaliplatin or bevacizumab, experienced increased rates of grade 3 or 4 toxicity [9–11, 43, 45]. On the other hand, mistletoe extract with chemotherapeutical regimes for solid tumors can improve in health related quality of life [15, 47]. Mistletoe extract reduced the rate of gastrointestinal adverse effects such as diarrhea in gastric cancer during adjuvant chemotherapy [15]. In the present study, all adverse events, including gastrointestinal symptoms, oral mucositis, and peripheral neuropathy, were grade I. Only NMG had grade II neutropenia, and grade III anemia; on the other hand, pruritus was observed in MG. There were no statistical differences between MG and NMG. It shows that mistletoe extract is safe and less toxic agents for the treatment of rectal cancer patients at NCRT. Mistletoe extracts help reduce chemotherapy-induced toxicity and enhance treatment tolerability.

Our study had some limitations. First, the number of patients who received NCRT may not be enough to analyze the effect of mistletoe extract for locally advanced rectal cancer. We had practical constraints of patients' financial strain because the mistletoe extract does not be reimbursed under the national insurance system. Second, this is a retrospective nonrandomized study. Third, downstaging assessment of rectal tumor after NCRT has unavoidable limitations in its accuracy because the evaluation of preoperative tumor staging was based on image studies. Fourth, it is not fully known how mistletoe extract works to tumor regression. Nevertheless, the strength of this study is significant in that it is the first study to achieve good results using mistletoe extract together during NCRT for locally advanced rectal cancer.

Conclusions

Neoadjuvant chemoradiation with Abnoba Viscum Q® showed better tumor response for rectal cancer than conventional chemoradiation. Further large populated prospective randomized studies with long-term follow-up will be required to confirm the effectiveness of mistletoe extract in chemoradiation for patients with locally advanced rectal cancer.

Abbreviations

NCRT, neoadjuvant chemoradiotherapy

pCR, pathologic complete response

TRG, tumor regression grade

BMI, body mass index

ASA, American Society of Anesthesiologist

AJCC, American Joint Committee on Cancer

yp pathological status after NCRT

Declarations

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Authors' contributions

JHB designed the study. JHB, YJ, and KWH performed the data acquisition. JHB, YJ, KWH and KOK performed the data analysis and interpretation. JHB and YJ prepared the manuscript. JHB, YJ, KWH and KOK revised the paper critically. The authors read and approved the final manuscript.

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Availability of data materials

All data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The institutional review board of Gil Medical Center approved this retrospective observational study and waived the requirement for patient informed consent (IRB number GFIRB2020-304).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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