Radiofrequency thermal treatment with chemoradiotherapy for advanced rectal cancer

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Abstract. We previously reported that patients with a clinical complete response (CR) following radiofrequency thermal treatment exhibit significantly increased body temperature compared with other groups, whereas patients with a clinical partial response or stable disease depended on the absence or presence of output limiting symptoms. The aim of this study was to evaluate the correlation among treatment response, Hidaka radiofrequency (RF) output classification (HROC: termed by us) and changes in body temperature. From December 2011 to January 2014, 51 consecutive rectal cancer cases were included in this study. All patients underwent 5 RF thermal treatments with concurrent chemoradiation. Patients were classified into three groups based on HROC: with ≤9, 10-16, and ≥17 points, calculated as the sum total points of five treatments. Thirty-three patients received surgery 8 weeks after treatment, and among them, 32 resected specimens were evaluated for histological response. Eighteen patients did not undergo surgery, five because of progressive disease (PD) and 13 refused because of permanent colostomy. We demonstrated that good local control (ypCR + CR + CRPD) was observed in 32.7% of cases in this study. Pathological complete response (ypCR) was observed in 15.7% of the total 51 patients and in 24.2% of the 33 patients who underwent surgery. All ypCR cases had ≥10 points in the HROC, but there were no patients with ypCR among those with ≤9 points in the HROC. Standardization of RF thermal treatment was performed safely, and two types of patients were identified: those without or with increased temperatures, who consequently showed no or some benefit, respectively, for similar RF output thermal treatment. We propose that the HROC is beneficial for evaluating the efficacy of RF thermal treatment with chemoradiation for rectal cancer, and the thermoregulation control mechanism in individual patients may be pivotal in predicting the response to RF thermal treatment.

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Key words: rectal cancer, radiofrequency thermal treatment, chemoradiation, Hidaka RF output classification, thermoregulation

Introduction

Hyperthermia has a long history and is widely used in various medical fields (1). Radiofrequency (RF) hyperthermia (HT) has been performed in Japan and is associated with two major issues: i) this modality has not been approved as a standardized treatment in oncology, and ii) there is a risk of a fatal complication, the hot spot phenomenon, which is induced by RF thermal therapy itself (2,3). Many randomized trials of HT have demonstrated a significant improvement in clinical outcome for several tumor types (4-6). However, due to the lack of standardization parameters, and absence of a reference point for this therapy, clinical studies have had contradictory outcomes, thereby raising doubts about efficacy.

Conversely, rectal cancer shows higher local recurrence rates than colon cancer after surgery (7-9). Since the National Comprehensive Cancer Network Practice Guidelines for treatment of primary rectal cancer were specified in 2009, neoadjuvant chemoradiation (NACR) has been accepted as the standard therapy worldwide, except in Japan. Many studies have demonstrated that NACR increases local control but exerts no influence on overall survival (10-12). New strategies that incorporate neoadjuvant therapy are required for rectal cancer.

We reported that hyperthermo-chemoradiotherapy (HCRT) for rectal cancer is performed safely (13). The main endpoint of this study was the evaluation of the pathological and clinical responses after HCRT using the Hidaka RF output classification (HROC: termed by us).

Materials and methods

Between December 2011 and January 2014, 51 consecutive patients with primary rectal cancers were included in this

study. Patients received pre-treatment and post-treatment diagnostic examinations, including computed tomography (CT), positron emission tomography/CT (PET/CT), and magnetic resonance imaging (MRI), at Hidaka Hospital. The extent and location of the tumor were classified according to the tumor-node-metastasis TNM staging (14). Patients underwent HCRT at Hidaka Hospital. Operations were performed at the Department of General Surgical Science, Gunma University, or at the Division of Surgery, Hidaka Hospital. Each resected specimen was evaluated histologically at the Department of Pathology, Gunma University. The study was approved by the Ethics Committees of the Hidaka Hospital and Gunma University. Each patient gave written informed consent prior to enrollment in the study.

Chemoradiotherapy. Intensity-modulated radiotherapy was administered conventionally once daily 5 times/week using TomoTherapy® (Hi-Art® treatment system; Accuray). Neoadjuvant radiotherapy (NART) consisted of 50 Gy delivered to the posterior pelvis in 25 fractions of 2 Gy each. Concurrent neoadjuvant chemotherapy was delivered in 5-day courses during the first to fifth weeks of NART. Capecitabine was administered orally at a dose of 1,700 mg/m^2/day.

Hyperthermia. RF thermal treatment was performed using the Thermotron-RF 8 (Yamamoto Vinita Co., Ltd., Japan) and administered once a week for 5 weeks with a 50-min irradiation. From December 2011 to November 2012, 19 patients underwent abdominal hyperthermia treatment and the RF output was retrospectively evaluated and from November 2012 to January 2014, 32 patients prospectively received a standardized increasing output method (which we termed neothermia) based on retrospective data. Details of the method for increasing output have been reported previously (15). Briefly, group A included patients with a thickness of fat of the abdominal wall <16 mm, visceral fat area <100 cm^2 and total fat area <190 cm^2, and group B included patients with either one of the aforementioned factors. For patients in group A, the output was increased to 50 W/min, whereas patients in group B received 25 W/min. The operator started the output from 200 W and increased to 1,200 W until output limiting symptoms occurred and then decreased the output by 100 W. Most patients did not complain and continued the first RF thermal treatment. Subtracting 100 W output was judged as the optimal energy output dose without output limiting symptoms. From the second to fifth RF thermal treatment, this output was applied for 50 min. These principles were maintained in patients with neothermia in this prospective study.

Thermal output. A sensor catheter with 4 temperature points was placed in the rectum of 12 patients while it was attached to the skin on the lateral abdominal side, as well as in 39 patients who received neothermia and in 7 who did not. The accumulated thermal output was calculated from the estimated internal temperature of patients during the 50-min duration of each irradiation. An increased thermometric scale of the skin and the rectum was added to the pretreatment axillary temperature of the patients to obtain a hypothetical internal body temperature. Temperature and output curves were recorded at 1-min intervals from treatment initiation to completion (50 min).

Table I. Patient characteristics.

Characteristics	Data
Total no. of patients	51
Age (years)	
Median	62
Range	33-89
Gender, n (%)	
Female	13 (25.5)
Male	38 (74.5)
Stoma, n (%)	
(-)	41 (83.7)
(+)	8 (16.3)
Tumor location, n (%)	
Ra	5 (9.8)
Rb	30 (58.8)
RbP	15 (29.4)
P	1 (2.0)
Primary tumor, n (%)	
T2	9 (17.6)
T3	36 (70.6)
T4	6 (11.8)
Regional lymph node status, n (%)	
N(-)	30 (58.8)
N(+)	21 (41.2)
Distant metastasis, n (%)	
M0	46 (90.2)
M1	5 (9.8)
TNM stage[a], n (%)	
Stage 1	7 (13.7)
Stage 2	21 (41.2)
Stage 3	18 (35.3)
Stage 4	5 (9.8)
Tumor differentiation, n (%)	
Well differentiated	27 (52.9)
Moderately different	21 (41.2)
Poorly differentiated	3 (5.9)
A-V distance (cm)	
Median	3.0
Average (± SE)	2.70 (0.33)

[a]Pretreatment tumor staging was clinical, if available, by CT and MR.

RF output. Details of the HROC have been reported previously (15). Briefly, the total accumulated irradiation output (W/min) was classified into four groups: ≤26,000, 260,001-32,600, 32,601-39,500, and ≥39,501, as 1 point, 2 points, 3 points, and 4 points, respectively. The HROC was further classified into three groups: ≤9, 10-16, and ≥17 points, which were the sum of the five treatments.

Evaluation of objective response. All patients were evaluated according to the Response Evaluation Criteria in Solid

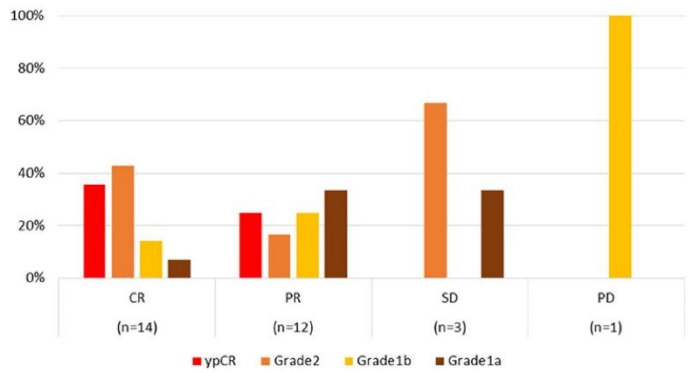


Figure 1. Discrepancies between clinical and histological objective responses. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ypCR, pathological complete response.

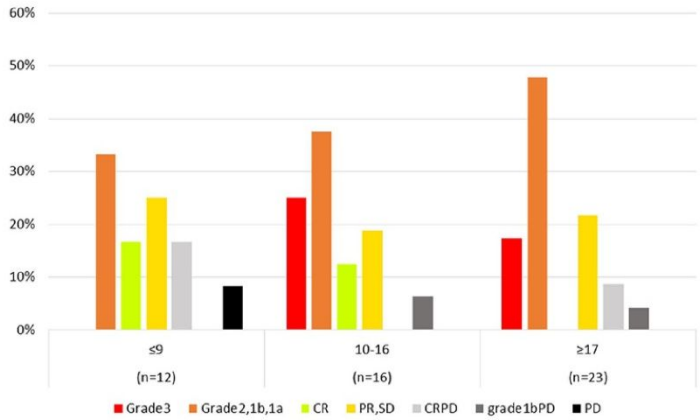


Figure 2. Results of the correlation between the objective response and the Hidaka RF output classification (HROC). CR, complete response; PR, partial response; SD, stable disease; CRPD, local CR but distant PD; PD, progressive disease. Grade; pathological complete response (pCR), grade 1bPD; local grade 1b but PD.

Tumors using MRI and PET/CT (16). Each resected specimen was examined for histological changes based on the histological criteria of the Japanese Classification of Colorectal Carcinoma. The CRPD group included patients in whom local tumors showed a complete response (CR), although new distant metastasis appeared. For the response assessment 8 weeks after HCRT, we evaluated CR as disappearance of the tumor on PET/CT and MRI and a positive to negative change in PET/CT. Adverse effects of these treatments were evaluated based on the criteria defined by the Common Terminology Criteria for Adverse Events (17).

Statistical analysis. SPSS Statistics (IBM, Armonk, NY, USA) version 21 was used to analyze all data. Mean values were compared using the Student's t-test. All reported p-values are two-tailed and were considered significant at $P<0.05$.

Results

Table I shows the patient characteristics. One patient had grade 3 perianal dermatitis. Only 2 patients with grade 2 disease wanted to decrease the dose of capecitabine (complete treatment, 96.1%). No output limiting symptoms were observed in 63.5% of the patients, whereas 30.2% suffered pain, and 2.0% had subcutaneous induration.

Good local control (ypCR + CR + CRPD) was observed in 32.7% of the patients in this study. Pathological complete response (ypCR) was observed in 15.7% of the total 51 patients and in 24.2% of the 33 patients who underwent surgery. Patients underwent surgery 8 weeks after HCRT. Abdominoperitoneal resection, lower anterior resection, intersphincteric resection, and partial resection were performed in 25, 43.7, 21.9, and 9.4% of the patients, respectively. One patient could

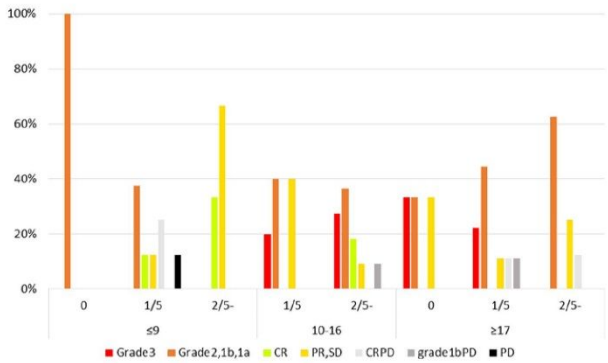
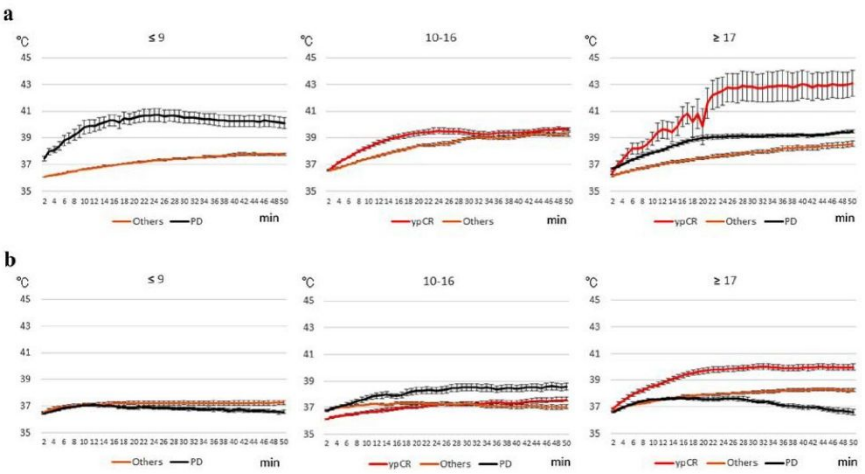


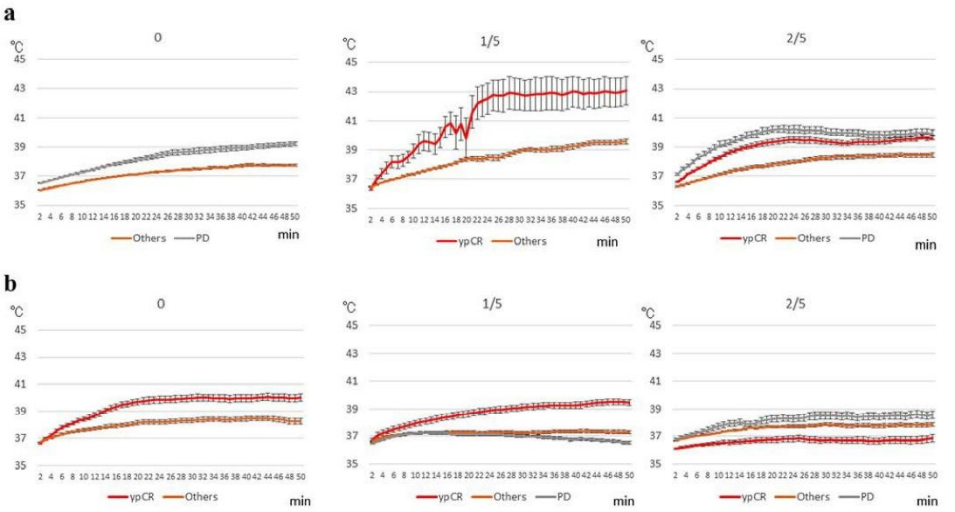
Figure 3. Results of the correlation among the objective response, the Hidaka RF output classification (HROC), and the incidence of output limiting symptoms. No output limiting symptoms, 1 output limiting symptoms, and ≥2 output limiting symptoms during the 5 thermal treatments are represented as 0, 1/5 and 2/5, respectively. CR, complete response; PR, partial response; SD, stable disease; CRPD, local CR but distant PD; PD, progressive disease. Grade; pathological complete response (pCR), grade 1bPD; local grade 1b but PD.



		Rectum	Time (min)	Skin	Time (min)
HROC	≤9	Others vs. PD	0-50	Others vs. PD	48-50
	10-16	ypCR vs. others	1-29	PD vs. ypCR	0-50
				PD vs. others	0-50
				ypCR vs. others	1-17
	≥17	ypCR vs. PD	0-50	ypCR vs. PD	0-50
		ypCR vs. others	0-50	ypCR vs. others	0-50
		Others vs. PD	0-50	Others vs. PD	31-50

Figure 4. Changes in rectal and skin temperatures during RF thermal treatment. (a) Rectal temperatures and (b) skin temperatures. Others: minor response [grade 2 + 1b + 1a + complete response (CR) + partial response (PR) + stable disease (SD)]. The results are presented as means ± standard errors. Significant differences were achieved (see table above) ($P<0.05$). PD, progressive disease; ypCR, pathological complete response.

not undergo resection of the primary tumor, and 5 patients could not undergo surgery due to progressive disease (PD); 13 (3 CR and 10 PR, SD) patients refused surgery mainly due to a permanent colostomy. Complete pathological response



		Rectum	Time (min)	Skin	Time (min)
Incidence of output limiting symptoms	0	PD vs. others	0-5	ypCR vs. others	0-50
	1/5	ypCR vs. others	0-50	ypCR vs. others	0-50
				ypCR vs. PD	0-50
				Others vs. PD	36-50
	2/5	PD vs. ypCR	1-34	PD vs. ypCR	0-50
		PD vs . others	0-50	PD vs. others	-
		ypCR vs. others	0-50	PD vs. others	8-15

Figure 5. Changes in rectal and skin temperatures during irradiation (50 min) based on the incidence of output limiting symptoms and the objective response. (a) Rectal temperatures and (b) skin temperatures. The results are presented as means ± standard errors. Significant differences were achieved (see table above) ($P<0.05$). PD, progressive disease; ypCR, pathological complete response.

(ypCR), grade 2, grade 1b, and grade 1a were observed in 25.0, 31.3, 21.9, and 18.8% of 32 patients, whose tumors were resected, respectively. Two patients with grade 1b showed PD. A change from T2 to T0 was observed in 66.7%, T3 to T2 and T0 in 69.4%, T4 to T2 and T3 in 50.0%, N(+) to yN(-) in 66.7%, and M0 to M1 in 8.7% of the patients.

Fig. 1 illustrates the discrepancies between clinical and histological responses; CR and partial response (PR) were observed in 35.7 and 25.0% of patients showing ypCR, respectively, whereas no ypCR was observed in patients with both stable disease (SD) and PD.

Fig. 2 illustrates the results of the correlation between objective response and the HROC. Eight patients with ypCR presented with ≥10 points, whereas 4 patients with PD also presented with ≥10 points. There was no patients with ypCR among those with ≤9 points in the HROC.

Fig. 3 shows the results of the correlation between objective response, the HROC, and the incidence of output limiting symptoms. Patients with ypCR either experienced output limiting symptoms or were free of output limiting symptoms. PD was not observed in patients with ≥17 points without output limiting symptoms, whereas ypCR was not observed in patients with ≤9 points. Three patients with PD (CRPD+grade 1bPD) and output limiting symptoms presented with ≥17 points.

Fig. 4 illustrates the changes in rectal (Fig. 4a) and skin (Fig. 4b) temperatures during RF thermal treatment for 50 min, based on the HROC and objective response. For ≤9 points, the rectal temperature of PD patients was increased significantly when compared with the rectal temperature of the others, while, skin temperature of the others was slightly increased. For 10-16 points, the rectal temperature of the ypCR patients was significantly increased when compared with the rectal temperature of the others, while, skin temperatures of the PD patients was significantly increased when compared with skin temperatures of patients with pyCR and others ($P<0.05$). In regards to ≥17 points, rectal and skin temperatures of the ypCR patients were significantly increased when compared with these temperatures of others and PD ($P<0.05$).

Fig. 5 shows the changes in rectal (Fig. 5a) and skin (Fig. 5b) temperatures during RF treatment for 50 min, based on the incidence of output limiting symptoms and objective response. In patients without output limiting symptoms, rectal temperature

of the PD patients was significantly increased than those of others, while skin temperature of the ypCR patients was significantly increased when compared with the skin temperature of the others ($P<0.05$). In patients who suffered output limiting symptoms once during the 5 treatments, both rectal and skin temperatures of the ypCR patients were significantly increased when compared with those of the other responses ($P<0.05$). However, in patients who experienced output limiting symptoms ≥2 times, both rectal and skin temperatures of the PD patients showed significantly higher temperature increases than those with others and ypCR ($P<0.05$).

Based on the results of Figs. 4 and 5, two types of patients were identified: patients with or without increased temperatures, and consequently, those who benefited or those who did not; and patients with or without increased temperatures in both the ypCR and PD groups, even though they received similar RF outputs.

Discussion

In this retrospective and prospective study, we aimed to establish a standardized protocol for RF hyperthermia safety, and 15.7, 7.8, and 7.8% of patients experienced ypCR, CR, and CRPD, respectively; 31.4 and 13.7% of patients showed good local control (ypCR + CR + CRPD) and PD (CRPD + grade 1b PD + PD), respectively. All ypCR cases had ≥10 points, while no ypCR patients presented with ≤9 points according to the HROC. We also demonstrated that there were two types of patients: patients with or without increased temperatures and who consequently received a benefit or not from treatment, even though they received similar RF outputs. Previously, we had reported that all patients with clinical CR showed significantly higher increases in temperatures than those with other responses, whereas in PR + SD patients the increase of temperature or not depended on whether the patients experienced any output limiting symptoms or not, and consequently, had good or poor outcomes (15). Our results indicate that increased temperatures correlate with the clinical response but not the histological response; increased temperatures served to control tumors but not kill tumor cells.

Randomized NART for rectal cancer showed a ypCR rate ranging from 13 to 20%, with grade 3 toxicity ranging from 6 to 25% (18). Oxaliplatin-based neoadjuvant chemotherapy resulted in an increase in ypCR rates and grade 3 toxicity (19-21). For rectal cancers, NART plus capecitabine showed a ypCR rate ranging from 6.7 to 31%, with grade 3 toxicity ranging from 5 to 15% (22). Capecitabine plus IRMT showed a ypCR ranging from 14.1 to 30.6%, with grade 3 toxicity ranging from 11.1 to x17.6% (23). Lu *et al* reported a ypCR rate of 20%, grade 3 toxicity of 22%, and PD rates of 17% (24). Whereas NACR showed superior local tumor control and higher rates of side effects than our results, most studies failed to report PD cases.

The correlation between the efficacy of hyperthermia and temperature has been reported (25). Based on our results and other reports of NART, the following two questions were raised: i) no ypCR was observed among patients with ≤9 points, and ii) ypCR patients did not have increased temperature, but had a good outcome. These questions may be pivotal in predicting the response to hyperthermia based on the control mechanism of a set point of core temperatures and thermoregulation in individual patients.

In this study, we analyzed skin temperature as a simple reproducible marker. Thermal control of skin temperature depended on a fundamental homeostatic function. Therefore, skin thermoregulation depends on the thermoregulatory center and thermoreceptors on the skin (26). Recently an association was observed between thermoregulation and the transient receptor potential (TRP) family; TRP vaniloid-1 was one of the important factors for thermoregulation and was activated at a noxious heat range (>43˚C) or at temperatures above 32˚C, and it was correlated with pain threshold (27-29). The correlation between the TRP family and thermal treatment will be considered in the future.

In conclusion, we proposed a standardization of RF thermal treatment safety. Neothermia with chemoradiation is a potential new treatment for rectal cancer; further studies on preventing output limiting symptoms and evaluating thermoregulatory control mechanisms in individual patients are needed in the future.

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Outcome of laparoscopic gastrectomy with D1 plus lymph node dissection in gastric cancer patients postoperatively diagnosed with locally advanced disease or lymph node metastasis

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Abstract
Background Some laparoscopic gastrectomy (LG) patients are postoperatively diagnosed with locally advanced disease or lymph node metastasis. Few reports have reviewed the outcomes or validity of LG in such patients.
Methods We retrospectively compared the outcomes of LG for gastric cancer patients postoperatively diagnosed with T3 (subserosal invasion) or higher or N1 (metastasis in 1–2 regional lymph nodes), or higher disease ($n = 36$), with open gastrectomy (OG) for c-stage I gastric cancer patients ($n = 62$).
Results D1 plus lymph node dissection was performed in all patients in the LG group. Blood loss was significantly lower in the LG group than in the OG group ($P < 0.0010$). The mean postoperative hospital stay duration was significantly shorter in the LG group than in the OG group ($P = 0.0016$). In the LG group, lymph node metastasis occurred in 1 patient, peritoneal dissemination in 2 patients, and liver metastasis in 1 patient. The 5-year survival rate did not significantly differ between the LG and OG groups (90.00 vs. 94.52 %; $P = 0.6517$).
Conclusions Given the similarity in long-term outcomes between the LG and OG groups, LG is an appropriate indication for gastric cancer patients postoperatively diagnosed with locally advanced disease or lymph node metastasis.

Keywords Laparoscopic surgery · Gastric cancer · Diagnosis · Retrospective study

Since the first report in the 1990s [1], laparoscopic surgery for gastric cancer has been performed at many institutions. Improvements in the laparoscopic gastrectomy (LG) procedure and equipment have reportedly increased the safety and reduced the invasiveness of this surgical approach [2, 3]. According to a survey conducted by the Japan Society for Endoscopic Surgery and the statistical database of the Ministry of Health, Labour, and Welfare of Japan, a laparoscopic approach is used in approximately 20 % of gastric cancer surgeries. A consensus has not been reached regarding the indication of LG for advanced gastric cancer because of the difficulty in performing D2 lymph node dissection and insufficient evidence regarding long-term outcomes. At our institution, LG for gastric cancer was introduced in 1997, and we have recently performed this procedure for patients with relatively early stages of disease, such as T2 (tumor invasion into the muscularis propria) or lower and N0 (no lymph node metastasis) disease. However, in some cases, patients were postoperatively diagnosed with locally advanced disease (T3 or higher) or lymph node metastasis (N1 or higher). Therefore, the objective of this study was to evaluate the outcomes and validity of LG in these cases.

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Materials and methods

Case series

This study was conducted from January 2005 to December 2011 at the Department of General Surgical Science, Gunma University Graduate School of Medicine. We performed LG or open gastrectomy (OG) for 578 gastric cancer patients (LG, $n = 270$; OG, $n = 285$). Of these 270 LG patients, 37 who were postoperatively diagnosed with locally advanced disease (T3 or higher but not stage IV) or lymph node metastasis (N1 or higher) were selected. One patient who underwent treatment for malignant lymphoma was excluded from the analysis. Therefore, 36 patients were included in the retrospective analysis. Of these 285 OG patients, 62 patients who underwent OG for c-stage I gastric cancer were also included in the analysis for comparative purposes (Fig. 1). No patients received adjuvant therapy prior to surgery. LG was performed on gastric cancer patients with T2 or lower and N0 disease. OG was performed for c-stage I gastric cancer patients because of advanced age, obesity, abdominal surgery history, or patient request. All gastric cancer patients underwent a preoperative endoscopic ultrasound to diagnose the degree of tumor invasion. Gastric cancer stage was determined according to the Classification of Gastric Carcinoma (third edition) of the Japanese Gastric Cancer Association [4]. The procedures used in this study were approved by the Institutional Review Board of Gunma University Hospital. Written informed consent was obtained from all the patients.

LG procedure

All LG patients were placed in a supine position with the legs abducted. Normally, 5 ports were used. D1 plus lymph node dissection was performed in all LG patients according to the protocols outlined in the 2010 Japanese Gastric Cancer Treatment Guidelines [5]. Removal of the resected specimen and reconstruction were performed through a small abdominal incision approximately 4–5 cm in length.

Regarding reconstruction after distal gastrectomy, Billroth I reconstruction was our first choice. For patients with a small remnant stomach or hiatal hernia or for cases in which gastric cancer had invaded the bulbus of the duodenum, Roux-en-Y reconstruction was selected. Before 2008, the surgeon selected Billroth II reconstruction for distal OG in some gastric cancer cases. More recently, we performed Roux-en-Y anastomosis with the OrVil™ device (Medtronic, Inc., Minneapolis, MN, USA) for subtotal or near-total gastrectomy and removed the resected specimen through an extended navel incision.

Statistical analysis

All data are presented as mean ± standard error. Differences between the LG and OG groups were analyzed using Student's t and Pearson's Chi-squared tests. A P value < 0.05 was considered significant. Survival rates were determined using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using JMP 5.0 software (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics

The characteristics of patients in the LG and OG groups are shown in Table 1. The mean age was significantly lower in the LG group than in the OG group ($P = 0.0087$). No significant differences in sex, tumor location, macroscopic resected specimen type, or operative method were observed between the 2 groups ($P = 0.4292$, $P = 0.0665$, $P = 0.0529$, and $P = 0.1279$, respectively). The reconstruction methods differed significantly between the 2 groups, however ($P = 0.0258$). All 36 patients in the LG group underwent D1 plus lymph node dissection. In the OG group, D1 dissection was performed in 23 patients, D1 plus

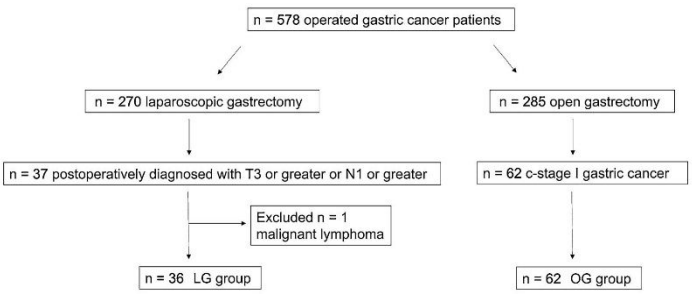

Fig. 1 Case series. We compared 25 LG group patients who were postoperatively diagnosed with locally advanced disease (T3 or higher but not stage IV) or lymph node metastasis (N1 or higher) with 55 OG patients who underwent OG for c-stage I gastric cancer. *LG* laparoscopic gastrectomy, *OG* open gastrectomy

Table 1 Patient characteristics

	LG ($n = 36$)	OG ($n = 62$)	P value
Age	60.1 ± 1.9	66.5 ± 1.4	0.0087
Sex			0.4292
Male	24	46	
Female	12	16	
Tumor location			0.0665
U	9	13	
M	19	21	
L	8	28	
Macroscopic type			0.0529
I	0	3	
IIa	3	8	
IIb	1	3	
IIc	18	38	
III	0	1	
Type 1	2	4	
Type 2	3	1	
Type 3	2	4	
Type 4	2	0	
Type 5	3	0	
Post-ESD	2	0	
Operative method			0.1279
Distal gastrectomy	25	30	
Proximal gastrectomy	7	21	
Total gastrectomy	4	11	
Reconstruction			0.0258
B-I	23	25	
B-II	0	2	
R-Y	6	15	
Gastric tube	7	9	
J-inter	0	11	
Lymph node dissection			<0.001
D1	0	23	
D1+	36	10	
D2	0	29	

ESD endoscopic submucosal dissection, *L* lower region of the stomach, *LG* laparoscopic gastrectomy, *M* middle region of the stomach, *OG* open gastrectomy, *U* upper region of the stomach, *B-I* Billroth I reconstruction, *B-II* Billroth II reconstruction, *R-Y* Roux-en-Y reconstruction, *J-inter* jejunal interposition

dissection in 10 patients, and D2 dissection in 29 patients ($P < 0.001$).

Operation outcomes

The operation outcomes for the LG and OG groups are shown in Table 2. The mean operation time did not significantly differ between the 2 groups ($P = 0.4278$), with times of 199.0 ± 7.5 min in the LG group and 191.7 ± 5.7 min in the OG group. Blood loss was significantly lower in the LG group than in the OG group (110.0 ± 29.1 vs. 288.4 ± 22.2 ml; $P < 0.001$). The mean number of dissected lymph nodes was significantly higher in the LG group than in the OG group (31.6 ± 2.2 vs. 24.5 ± 1.7; $P = 0.0131$). Additionally, the mean postoperative hospital stay duration was significantly shorter in the LG group than in the OG group (12.3 ± 1.3 vs. 16.6 ± 0.9 days; $P = 0.0016$).

Pathological findings

The pathological findings for the LG and OG groups are shown in Table 3. In the LG group, 14 patients (38.9 %) had differentiated-type gastric cancer and 22 patients (61.1 %) had undifferentiated-type gastric cancer. In the OG group, 43 patients (69.4 %) had differentiated-type gastric cancer and 19 patients (30.6 %) had undifferentiated-type gastric cancer. The number of undifferentiated-type cases was significantly higher in the LG group than in the OG group ($P = 0.0032$). The number of patients with venous invasion was also significantly higher in the LG group than in the OG group [15/36 (41.7 %) vs. 13/62 (21.0 %); $P = 0.0288$]. Additionally, the number of patients with lymphatic invasion was also significantly higher in the LG group than in the OG group [30/36 (83.3 %) vs. 22/62 (35.5 %); $P < 0.001$]. Early cancer limited to the mucosa or submucosa was significantly more common in the OG group than in the LG group ($P = 0.0007$). The lymph node metastasis rate was significantly higher in the LG group than in the OG group ($P < 0.001$), with rates of 86.1 % (31/36) in the LG group and 23.6 % (10/62) in the OG group. The pathological stage was also significantly more advanced in the LG group than in the OG group ($P < 0.001$).

Postoperative complications

Postoperative complications in the LG and OG groups are shown in Table 4. In the LG group, anastomotic stricture occurred in 5 patients (13.9 %), ileus-related complications in 1 patient (4.0 %), and other complications in 2 patients (5.6 %). In the OG group, wound infection occurred in 2 patients (3.2 %), anastomotic leakage in 3 patients (4.8 %), anastomotic stricture in 2 patients (3.2 %), intra-abdominal abscess in 3 patients (4.8 %), ileus-related complications in 1 patient (1.6 %), pancreatic fistula in 1 patient (1.6 %), and respiratory complications in 2 patients (3.2 %). Overall, 8 patients (22.2 %) in the LG group and 14 patients (22.3 %) in the OG group experienced postoperative complications. Although a tendency toward fewer postoperative complications (except anastomotic stricture) was

Table 2 Operation outcome

	LG ($n = 36$)	OG ($n = 62$)	P value
Operation time (min)	199.0 ± 7.5	191.7 ± 5.7	0.4278
Blood loss (ml)	110.0 ± 29.1	288.4 ± 22.2	<0.001
Number of dissected lymph nodes	31.6 ± 2.2	24.5 ± 1.7	0.0131
Duration of postoperative hospital stay (days)	12.3 ± 1.3	16.6 ± 0.9	0.0016

LG laparoscopic gastrectomy, *OG* open gastrectomy

Table 3 Pathological findings

	LG ($n = 36$)	OG ($n = 62$)	P value
Histological type			0.0032
Differentiated	14	43	
Undifferentiated	22	19	
Capillary invasion			
v+	15	13	0.0288
ly+	30	22	<0.001
Depth of invasion			0.0007
pM	1	21	
pSM	17	30	
pMP	6	5	
pSS	3	4	
pSE	8	2	
pSI	0	0	
No residual tumor	1	0	
Lymph node metastasis			<0.001
pN0	5	52	
pN1	18	8	
pN2	11	1	
pN3	2	1	
Stage			
IA	0	47	<0.001
IB	12	8	
IIA	14	1	
IIB	2	4	
IIIA	3	0	
IIIB	4	0	
IIIC	1	1	
IV	0	1	

LG laparoscopic gastrectomy, *ly+* lymphatic invasion, *OG* open gastrectomy, *v+* venous invasion, *m* mucosa, *sm* submucosa, *mp* muscularis propria, *ss* subserosa, *se* serosa exposed, *si* serosa infiltrating

Table 4 Postoperative complications

	LG ($n = 36$)	OG ($n = 62$)	P value
Wound infection	0	2	0.2762
Anastomotic leakage	0	3	0.1801
Anastomotic stricture	5	2	0.0482
Intra-abdominal abscess	0	3	0.1801
Ileus	1	1	0.6942
Pancreatic fistula	0	1	0.4437
Respiratory	0	2	0.2762
Others	2	0	0.0608
Total	8	14	0.8569

LG laparoscopic gastrectomy, *OG* open gastrectomy

Table 5 Long-term outcomes

	LG ($n = 36$)	OG ($n = 62$)	P value
Recurrence			
Lymph node	1	0	0.1871
Peritoneal dissemination	3	1	0.1050
Distant metastasis			
Liver	1	2	0.9012
5-year survival rate	90.00 %	94.52 %	0.6517

LG laparoscopic gastrectomy, *OG* open gastrectomy

observed in the LG group relative to the OG group, the number of postoperative complications did not significantly differ between the 2 groups ($P = 0.8569$) (Table 4).

Regarding complications, for patients in the LG group with anastomotic stricture, the tumor location was the upper area in 2 cases and middle area in 3 cases. For both patients in the OG group with anastomotic stricture, the tumor location was in the upper area. Among patients with anastomotic leakage in the OG group, 2 and 1 case involved tumors located in the upper and middle areas, respectively. In other words, complications were more frequently observed in tumors with a relatively higher location. Regarding the type of anastomosis, in the LG group, 2 cases were treated via Billroth I reconstruction, 2 cases were treated via Roux-en-Y reconstruction, and 1 case underwent gastric tube reconstruction. In the OG group, 1 case was treated via jejunal interposition and 1 case underwent gastric tube reconstruction. In OG group patients with anastomotic leakage, the reconstruction methods were Billroth I reconstruction in 1 case, Roux-en-Y reconstruction in 2 cases, and gastric tube reconstruction in 1 case. The type of anastomosis might not correlate with complications such as leaks or strictures. No cases of

pancreatitis developed after lymph node dissection in the LG group. In the OG group, 1 patient developed pancreatitis after lymph node dissection. This was addressed with conservative treatment.

Long-term outcomes

Long-term outcomes in the LG and OG groups are shown in Table 5. Lymph node recurrence occurred in 1 patient (2.8 %), peritoneal dissemination in 2 patients (8.3 %), and liver metastasis in 1 patient (2.8 %) in the LG group, whereas peritoneal dissemination occurred in 1 patient (1.6 %) and liver metastasis in 2 patients (3.2 %) in the OG group. The lymph node recurrence, peritoneal dissemination, and liver metastasis rates did not significantly differ between the 2 groups ($P = 0.1871$, $P = 0.1050$, and $P = 0.9012$, respectively). The details of the 4 recurrent cases in the LG group are shown in Table 6. In the lymph node recurrence case, only the No. 16 lymph node was affected. Adjuvant chemotherapy with S-1 was administered to all patients. After confirming a recurrence, patients underwent a routine systemic chemotherapy regimen. Of the 4 patients with recurrent disease, 3 patients died and 1 is undergoing treatment. The 5-year survival rate did not significantly differ between the LG and OG groups (90.00 vs. 94.52 %; $P = 0.6517$; Fig. 2). In the LG group, we encountered 3 cases of mortality, as shown in Table 6. In the OG group, we encountered 5 cases of mortality. The median follow-up durations were 56.7 months in the LG group (interquartile range 12.1–60.0 months) and 57.6 months in the OG group (interquartile range 7.0–60.0 months).

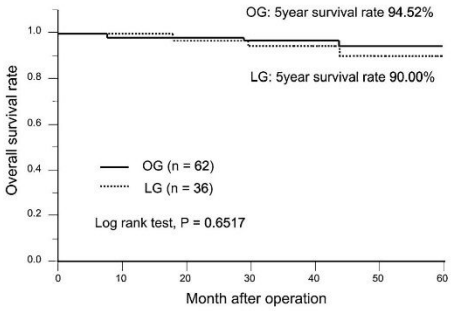

Fig. 2 Kaplan–Meier overall survival curves for the LG and OG groups. The 5-year survival rates did not significantly differ between the LG and OG groups (90.67 vs. 95.82 %; $P = 0.6406$). *LG* laparoscopic gastrectomy, *OG* open gastrectomy

Discussion

Since the initial report in the 1990s [1], laparoscopic surgery for gastric cancer has been performed at many institutions. Although several reports have demonstrated the safety and reduced invasiveness of this procedure, evidence concerning the long-term outcomes of LG remains insufficient [2, 3]. According to the 2010 Japanese Gastric Cancer Treatment Guidelines, LG should be considered an investigational treatment for stage IA and IB cancers [5]. Recently, some institutions have gradually expanded the indications for LG to include obese patients and those with advanced gastric cancer. In some cases, LG patients have been postoperatively diagnosed with locally advanced disease (T3 or higher) or lymph node metastasis (N1 or higher). In the present study, we evaluated the outcome and validity of LG in such cases. Our study found similar outcomes with LG with D1 lymph node dissection for patients postoperatively diagnosed with locally advanced disease or metastasis and OG for c-stage I patients.

Similarities and dissimilarities were observed between the LG and OG groups in terms of the operation outcomes, including the operation time, number of resected lymph

Table 6 Recurrent cases in the LG group

Age (years)	Operation	Recurrence	Preoperative diagnosis			Postoperative diagnosis				Adjuvant chemotherapy	Outcome (months)
			T	N	Stage	His	T	N	Stage		
62	LAPG	Lymph node (No. 16)	T2 (MP)	N0	IB	por1	T4a (SE)	N2	IIIB	S-1	Dead (44)
39	LATG	Peritoneal dissemination	T2 (MP)	N0	IB	sig	T4a (SE)	N3	IIIC	S-1	Dead (30)
63	LADG	Peritoneal dissemination	SMT	N0	IB	tub2	T4a (SE)	N2	IIIB	S-1	Alive
57	LADG	Liver metastasis	T1b (SM)	N0	IA	tub2	T1b (SM)	N1	IB	None	Dead (18)

His histological type, *LADG* laparoscopic distal gastrectomy, *LAPG* laparoscopic proximal gastrectomy, *LATG* laparoscopic total gastrectomy, *LG* laparoscopic gastrectomy, *SM* submucosa, *MP* muscularis propria, *SE* tumor invasion contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity, *SMT* submucosal tumor

nodes, blood loss, and postoperative hospital stay duration. The mean operation times were similar between LG and OG patients. In contrast, previous studies have reported significantly longer mean operation times for LG, compared with OG [6, 7]. The similar operation times observed in our study might have been due to be the use of a stylized procedure and an improved needle loop retractor [8] to hold and retract the stomach. Furthermore, the mean number of resected lymph nodes was significantly higher in the LG group than in the OG group, although D1 plus lymph node dissection was performed in all LG group patients and D2 lymph node dissection was performed in approximately half of the OG group patients. This finding might have resulted from the characteristics of lymph node dissection, which include the membrane structure and dissection time for the zoom-viewing effect of laparoscopic surgery. Additionally, the amount of blood loss was significantly lower in the LG group than in the OG group, and the mean postoperative hospital stay duration was significantly shorter in the LG group than in the OG group. Our findings regarding the number of resected lymph nodes [6, 7, 9, 10], blood loss [6, 7, 11], and postoperative hospital stay duration [6, 7, 11] were consistent with those of previous studies comparing LG and OG. Together, our results confirm the reduced invasiveness of laparoscopic surgery.

In terms of reduced invasiveness, laparoscopic surgery offers advantages over open surgery, including a smaller incision, less damage to the abdominal wall, less exposure to external air in the intestine, and reduced intestinal manipulation. Patients who underwent laparoscopic surgery achieved early postoperative ambulation with a reduced incidence of adhesion [12]. Moreover, a lower incidence of respiratory complications, such as pneumonia and atelectasis, was observed in LG patients compared with OG patients because the former could easily produce sputum [13]. Although the total number of postoperative complications tended to be slightly lower in the LG group than in the OG group, this difference was not significant in our study. The use of a stylized LG procedure and the minimal invasiveness of laparoscopic surgery have tended to reduce the incidence of complications at our institution.

Four recurrent cases occurred in the LG group: 1 case of lymph node recurrence, 2 cases of peritoneal dissemination, and 1 case of liver metastasis. The lymph node recurrent case involved the No. 16 lymph node, which could not have been dissected even if the patient had undergone OG. Peritoneal dissemination might have increased because of serosal injury near the tumor as a result of forceps manipulation and abdominal cavity insufflation [14]. In this study, the peritoneal dissemination rate was slightly higher in the LG group than in the OG group. However, both peritoneal dissemination cases in the LG group were diagnosed as pathological SE (tumor invasion contiguous to the serosa or penetration of the serosa with exposure to the peritoneal cavity), and thus peritoneal dissemination might have occurred even if the patients had undergone OG. We further compared the peritoneal dissemination rates between LG patients and OG patients according to pathological stage matching and found no significant difference between the 2 groups (data not shown). Therefore, it is unclear whether laparoscopic surgery was responsible for the 2 cases of peritoneal dissemination in the LG group. Furthermore, local and port-site recurrences, which commonly occur after laparoscopic surgery, were not observed. Accordingly, the laparoscopic approach was appropriate for the 3 recurrent cases in the LG group.

The long-term prognosis of the LG group patients, all of who underwent D1 plus lymph node dissection, was similar to that of the OG group patients. The 5-year survival rate in the LG group was 90.00 %, which was not significantly different from that of the OG group. In the LG group, 21 patients received S-1-based adjuvant chemotherapy. Postoperative adjuvant therapy with S-1 has been confirmed to improve both overall and relapse-free survival in patients with stage II or III gastric cancer who have undergone D2 gastrectomy [15, 16]. Therefore, the similar survival rates of the 2 groups might have been achieved via S-1-based adjuvant chemotherapy. Of course, our finding does not deny the significance of D2 lymph node dissection. Many studies have reported similar long-term prognoses in patients with advanced gastric cancer who have undergone LG and OG with D2 lymph node dissection [6, 7, 9, 11]. Future prospective randomized controlled studies are needed to assess the validity of LG with D2 lymph node dissection for advanced gastric cancer.

Conclusions

Our study showed that LG with D1 lymph node dissection for patients with gastric cancer who were postoperatively diagnosed with locally advanced disease or metastasis yielded similar long-term outcomes to those of OG in c-stage I patients. Given the improvements in the LG procedure and equipment, the indications for LG should include advanced gastric cancer. However, minimally invasive procedures for D2 lymph node dissection and precise preoperative diagnosis should be developed. The limitations of the present study include its retrospective nature and the small number of patients. In the future, it will be necessary to confirm the long-term outcomes and validity of LG in patients with gastric cancer who are postoperatively diagnosed with locally advanced disease or lymph node metastasis through larger randomized controlled studies.

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Compliance with ethical standards

Disclosures Akiharu Kimura, Kyoichi Ogata, Norimichi Kogure, Toru Yanoma, Masaki Suzuki, Yoshitaka Toyomasu, Tetsuro Ohno, Erito Mochiki, and Hiroyuki Kuwano have declared no conflicts of interest or financial ties to disclose.

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