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Intraoesophageal pressure in patients receiving proximal gastrectomy with hinged double flap method for gastric cancer: a retrospective cohort study

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Background: Objective functional assessment of esophagogastric anastomosis in patients who underwent proximal gastrectomy with the hinged double flap method for gastric cancer has not been well investigated. This study aimed to perform a functional analysis of reconstruction using high-resolution impedance manometry (HRIM).

Materials and methods: The authors enroled 25 patients who underwent proximal gastrectomy for gastric cancer between May 2015 and April 2020 and subsequently underwent HRIM postoperatively. Eligible questionnaires [Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37)] were retrieved from 16 patients. The association between HRIM data and PGSAS-37 was analyzed.

Results: The amplitudes of distal oesophageal peristaltic waves, contractile front velocity, and distal latency assessed by HRIM were almost normal after surgery. Most patient's lower oesophageal sphincter (LES) resting pressure created by the hinged double flap was within normal limits. Conversely, LES residual pressure values during swallowing-induced relaxation were abnormally high in most patients, and the lower the values, the more severe the reflux and diarrhoea symptoms (P = 0.038, P = 0.041, respectively). In addition, even when the integrated relaxation pressure (IRP) was normal, lower values corresponded to more severe reflux symptoms (P = 0.020). The required LES pressure may be higher after proximal gastrectomy because of the relatively higher intragastric pressure due to the reduced volume of the remnant stomach. This also suggests that swallowing-induced relaxation of the LES was considered a trigger for oesophageal reflux in post-proximal gastrectomy patients.

Conclusion: LES residual pressure and IRP values in HRIM correlated with reflux symptoms in patients after proximal gastrectomy.

Keywords: gastric cancer, intraoesophageal pressure, postgastrectomy syndrome assessment scale-37, proximal gastrectomy

Introduction

Gastric cancer is the second leading cause of cancer-related death in both sexes worldwide^[1]. In recent years, early gastric cancer

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HIGHLIGHTS

- Objective functional assessment of the esophagogastric anastomosis in patients who have undergone proximal gastrectomy with the hinged double flap method for gastric cancer has not been well studied.
- This study objectively demonstrates the utility of the hinged double flap method for patients undergoing proximal gastrectomy using high-resolution impedance manometry.
- Lower oesophageal sphincter residual pressure and integrated relaxation pressure values in high-resolution impedance manometry correlated with reflux symptoms in patients after proximal gastrectomy.

has become an increasingly common indication for minimally invasive surgical treatment owing to advances in both mass screening and diagnostic techniques. Contrary to total gastrectomy as a standard procedure for treating upper gastric cancer, regardless of the stage of the disease, proximal gastrectomy has been used as a means to manage selected patients with early upper gastric cancer. This is because of its potential advantages, including maintenance of a gastric reservoir, higher quality of life (QOL) following surgery, avoidance of nutritional abnormalities, and body weight loss^[2,3].

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Among several reconstruction methods used following proximal gastrectomy, double-tract reconstruction, and esophagogastrostomy are commonly accepted^[4,5]. Except for the disadvantages such as anastomotic stricture and reflux esophagitis, esophagogastrostomy is the ideal and simplest reconstruction method following proximal gastrectomy. Kamikawa et al.^[6] established a novel esophagogastrostomy technique using the hinged double flap method to prevent reflux esophagitis. However, the cumbersome anastomoses of the intracorporeal hinged double flap method make the introduction of laparoscopic surgery difficult. Thus, we developed a novel technique of intracorporeal proximal gastrectomy that uses the V-Loc Absorbable Wound Closure Device (V-Loc; Covidien) and reported several advantages^[7]. In addition to our report, there are some reports of clinical advantages of esophagogastrostomy with the hinged double flap method following proximal gastrectomy^[4,8,9]. While clinical outcomes in patients undergoing proximal gastrectomy with the hinged double flap method have been well assessed, the anti-reflux mechanism in terms of intraeosophageal pressure remains unproven. This study objectively assessed the function of esophagogastric anastomosis in patients who underwent proximal gastrectomy with the hinged double flap and validated the usefulness of high-resolution impedance manometry (HRIM) after proximal gastrectomy with the hinged double flap method by applying the Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) to assess patient status^[10-13].

Methods

Ethics approval

This study was approved by the Institutional Review Board of our institution (No. E2019-1789-03) on 6 April 2023. The study protocol conformed to the provisions of the Declaration of Helsinki in 1995 (as revised in Brazil, 2013). Written informed consent was obtained from every patient at the initial visit. This case series has been reported in line with the STROCSS 2021 Guideline^[14]. The research was registered in ResearchRegistry. com. The UIN is researchregistry 7951.

This retrospective, single-centre, consecutive case series study included 25 patients (19 male and 6 female) who underwent proximal gastrectomy at our hospital between May 2015 and April 2020. All patients were preoperatively diagnosed with early gastric cancer. Tumour stage was classified according to the seventh edition of the International Union against Cancer tumour–node–metastasis staging system for gastric cancer, while lymph node stations were numbered according to the definitions of the Japanese Gastric Cancer Association^[15]. Operative complications were classified according to the Clavien–Dindo classification^[16].

Questionnaire survey

The integrated questionnaire Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37), newly designed by the Japan Postgastrectomy Syndrome Working Party, was used to assess a realistic image of the status of patients who received gastrectomy^[10]. It consists of 37 items, with 15 items from the Gastrointestinal Symptoms Rating Scale (GSRS), and 22 newly selected items. It is classified into three domains, that is, the symptom, living status, and QOL domains, each consisting of

several subdomains^[17]. The PGSAS statistic kit was used to compare the data with the values of the Japanese standards of the Proximal Gastrectomy cases obtained by the PGSAS study. Main outcome measures (symptom) in the symptom domain were rated on a 7-point Likert scale. Three items of the dissatisfaction subdomain were rated on a 5-point Likert scale. For items 1–8 and 38–40, higher scores indicated better conditions, whereas higher scores on items 9-28, 30, 31, 33, and 41–45 indicated poorer conditions.

High-resolution impedance manometry

All patients underwent HRIM, in which eight pressure sensors were spaced at 6-mm intervals along the catheter. The catheter was connected to a portable digital recorder device and eightchannel pressure data were recorded (Pocket Monitor GMMS-4000; Starmedical Inc.).

The catheter was inserted nasally under local anaesthesia. After the leading end of the catheter had reached the stomach, it was fixed in place by taping to the nose in a position. Ten wet swallows of 5 ml, spaced at 30 s intervals without swallowing, were given during the test in the dorsal position, after which the evaluation was carried out.

Postsurgical analysis was performed from 12 to 26 months after the operation. The amplitude of the distal oesophageal peristaltic waves was the mean pressure at 3 cm above the esophagojejunal junction (normal value 30-180 mmHg). The contractile front velocity (CFV) (normal value 2-8 cm/s) was defined as the slope of the line connecting the points on the 30 mmHg isobaric contour between the proximal pressure trough and contractile deceleration point. HRIM evaluates peristalsis by distal latency (DL) (normal value > 4.5 s), which is defined as the interval between upper oesophageal sphincter relaxation. The integrated relaxation pressure (IRP) (normal value <15 mmHg) is the mean of the lowest relaxation pressures measured within the LES for four contiguous or non-contiguous seconds during swallowing. This indicates the adequacy of LES relaxation. Two parameters are important for LES pressure: LES resting pressure which was defined as pressure at mid expiration (normal value, 10-45 mmHg) and LES residual pressure during swallowinginduced relaxation which was defined as the lowest 3 seconds mean LES pressure relative to intragastric pressure (normal value, <8 mmHg).

Statistical analysis

Statistical analyses were performed using JMP (version 10.0.2, SAS Institute Inc.).

Continuous data are expressed as median and interquartile (25-75th percentiles), unless otherwise indicated. For all tests, a two-sided *P* less than 0.05 was considered statistically significant.

Results

Patients' backgrounds

The patient background and surgical outcomes are listed in Table 1. Of the 25 patients (19 male and 6 female; median age, 68 years), 22 underwent laparoscopic proximal gastrectomy, two underwent robotic proximal gastrectomy, and one underwent open proximal gastrectomy. These individuals had a median body mass index of 22.4 kg/m² (range, 18.6–28.5). The median

 Table 1

 Preoperative data and clinical outcome of the patients

Case	Age	Sex	ECOG-PS	BMI	Operation method	Final TNM	Final stage*	Curability	Opening diaphragm	Operation time (min)	Blood loss (ml)	Discharge (POD)	Operative morbidity
1	76	F	1	22.8	LPG	T1N0M0	IA	RO	(—)	370	43	13	(-)
2	55	Μ	0	21.7	LPG	T1N0M0	IA	RO	()	370	10	13	(-)
3	70	Μ	0	23.9	LPG	T1N0M0	IA	R0	(—)	376	60	13	(—)
4	60	F	0	21.3	LPG	T1N0M0	IA	R0	(—)	338	50	12	(—)
5	63	F	0	28.1	LPG	T1N0M0	IA	RO	(—)	379	114	13	(—)
6	77	М	0	25.6	LPG	T2N2M0	IIB	RO	(—)	465	560	36	Grade II anastomotic leakage
7	60	Μ	0	22.8	LPG	T1N0M0	IA	RO	(—)	413	91	14	(-)
8	76	М	0	26.1	LPG	T1N0M0	IA	RO	(-)	427	193	13	(-)
9	63	Μ	0	28.0	LPG	T1N0M0	IA	RO	(-)	525	433	12	(-)
10	53	Μ	0	25.7	LPG	T1N0M0	IA	RO	()	271	10	13	(-)
11	80	Μ	0	23.1	LPG	T1N0M0	IA	R0	(—)	303	45	11	(—)
12	53	Μ	0	22.4	LPG	T1N0M0	IA	R0	(—)	470	120	13	(—)
13	80	F	0	28.5	LPG	T1N0M0	IA	R0	(—)	365	83	11	(—)
14	61	Μ	0	23.4	OPG	T1N0M0	IA	R0	(—)	305	123	11	(—)
15	65	Μ	0	23.8	LPG	T1N0M0	IA	RO	(—)	312	51	13	(—)
16	80	Μ	1	26.6	LPG	T1N0M0	IA	RO	(—)	513	306	12	(—)
17	63	F	0	22.4	LPG	T1N0M0	IA	RO	(—)	387	56	10	(—)
18	80	Μ	0	20.1	LPG	T1N0M0	IA	RO	(—)	335	30	10	(—)
19	71	Μ	0	18.6	LPG	T1N1M0	IB	RO	(—)	316	80	11	(—)
20	72	Μ	0	23.6	RPG	T1N0M0	IA	RO	(—)	379	26	10	(—)
21	66	Μ	0	24.6	LPG	T1N0M0	IA	RO	(—)	377	323	10	(—)
22	68	М	0	25.3	RPG	T1N0M0	IA	RO	(—)	395	34	28	Grade II pancreatic fistula
23	75	М	0	20.1	LPG	T1N0M0	IA	RO	(—)	333	126	11	Grade IIIa anastomotic stricture
24	66	М	1	20.8	LPG	T1N0M0	IA	R0	(—)	429	177	14	Grade II anastomotic stricture
25	75	F	0	20.6	LPG	T1N0M0	IA	RO	(—)	255	45	11	()

ECOG, eastern cooperative oncology group; F, female; LPG, Laparoscopic proximal gastrectomy; M, male; RPG, robotic proximal gastrectomy.

*Staging was performed according to the7th edition of the International Union against Cancer tumour-node-metastasis staging system for gastric cancer.

operation time was 376 min (range, 255–525 min) and blood loss was 56 ml (range, 10–560 ml). Surgical complications included one grade II minor anastomotic leakage, one grade II pancreatic fistula, and two grade II anastomotic strictures. The median length of hospital stay was 12 days (range: 10–36 days).

There was one case of recurrence during the 48.7-month median follow-up period (range 21.6–81.4 months).

High-resolution impedance manometry

The preoperative and postoperative peristaltic patterns of a representative case are shown in Fig. 1. After swallowing, the upper oesophageal sphincter relaxed and oesophageal peristaltic waves gradually propagated from the upper to the lower oesophagus. The LES relaxed temporarily after swallowing. The relaxation terminated when the peristaltic wave arrived. High pressure is indicated in red and low pressure in blue. The patient's peristaltic pattern showed no change from presurgery to post-surgery. Fig. 2. shows a detailed postoperative assessment at HRIM. The same peristaltic pattern as preoperatively was observed in the patients after proximal gastrectomy. The median amplitude of the distal oesophageal peristaltic waves was 52.2 (27.7–155.8), and that of the CFV was 3.0 (1.3–11.3) (Fig. 2A, B). In addition, the DL was normal in all patients (Fig. 2C). The amplitude values of the

distal oesophageal peristaltic waves, CFV and DL, which are indicators of oesophageal corpus movement, were almost normal. There was adequate pressure in almost all patients with good relaxation, as measured by a normal IRP (median: 11.1, 8.7–24.0) (Fig. 2D). The LES resting pressure was within normal limits in almost all patients (median: 27.2, 12–61.6) (Fig. 2E). In contrast, all patients showed abnormal LES residual pressure during swallowing-induced relaxation. The median pressure was 12.6 (8.1–36.7) (Fig. 2F).

Outcome measures in Postgastrectomy Syndrome Assessment Scale-37

Table 2 summarizes the mean values and standard deviations of the main outcome measures evaluated using the PGSAS-37. Using the PGSAS statistic kit, the data of our study were compared with the values of the Japanese standard data from the PGSAS study. The results of the PGSAS-37 score in this study were comparable to the values of patients who underwent proximal gastrectomy. The correlations between the three indices, IRP, LES resting pressure, and LES residual pressure as an assessment of LES and each subscale of the symptom domain were analyzed (Table 3). "Oesophageal reflux subscale" was significantly better with higher IRP (Fig. 3A). "Oesophageal reflux subscale" was significantly better in the abnormally high IRP group when analyzed



Figure 1. High-resolution impedance manometry findings. Preoperative and Postoperative high-resolution impedance manometry findings in a representative case. CFV, contractile front velocity; DL, distal latency; IRP, integrated relaxation pressure.

separately for the normal range and abnormally high IRP groups (Fig. 3B). The higher the value, the better the "Oesophageal reflux subscale" and "Diarrhoea subscale" symptoms were in the LES residual pressure where all patients had abnormally high values (Fig. 3C, D). One year postoperatively, "Quality of ingestion

subscale" affected the patients' weight loss and weight loss rate one year after surgery (r = -0.874, P = 0.0048, r = -0.876, P = 0.0044, respectively). The quality of ingestion assessed by the PGSAS-37 had a significant influence on patients' weight loss and weight loss rate one year after surgery.





Table 2				
Scores of th	e PGSAS-37	symptom at -	l vear after	surgerv

Domain	Item number (#)	Main outcome measures (symptom)	Control	Cases	P*
Symptoms	10, 11, 13, 24	Oesophageal reflux subscale	2.0 ± 1.0	1.7 ± 1.0	0.243
	9, 12, 28	Abdominal pain subscale	1.7 ± 0.7	1.6 ± 0.6	0.7
	25–27	Meal-related distress subscale	2.6 ± 1.1	2.7 ± 1.3	0.827
	14–17	Indigestion subscale	2.2 ± 0.8	2.2 ± 0.8	0.86
	19, 20, 22	Diarrhoea subscale	2.0 ± 1.0	1.9 ± 0.7	0.821
	18, 21, 23	Constipation subscale	2.3 ± 1.1	2.4 ± 1.4	0.737
	30, 31, 33	Dumping subscale	2.0 ± 1.0	2.2 ± 1.1	0.833
	9-28, 30, 31, 33	Total symptom score	2.1 ± 0.7	2.2 ± 0.8	0.94
Living status		Change in body weight (%)	-10.9 ± 8.2	-10.7 ± 5.8	0.906
0	34	Ingested amount of food per meal	6.5 ± 1.9	5.8 ± 2.6	0.185
	41	Necessity for additional meals	2.0 ± 0.8	2.3 ± 1.3	0.231
	38–40	Quality of ingestion subscale	3.6 ± 1.0	3.2 ± 1.4	0.166
	42	Ability for working	2.0 ± 0.9	1.6 ± 0.8	0.113
QOL	43	Dissatisfaction with symptoms	2.0 ± 0.9	1.8 ± 0.9	0.386
	44	Dissatisfaction at the meal	2.7 ± 1.1	2.8 ± 1.2	0.69
	45	Dissatisfaction at working	2.0 ± 1.1	1.9 ± 1.1	0.624
	43-45	Dissatisfaction for daily life subscale	2.2 ± 0.9	2.1 ± 0.9	0.52

PGSAS-37, Postgastrectomy Syndrome Assessment Scale-37; QOL, quality of life.

*Comparison between the data of proximal gastrectomy with hinged double flap method (n = 16) with the values of the Japanese standard data of the PGSAS study using the PGSAS statistic kit.

Discussion

Table 3

The ideal reconstruction methods after proximal gastrectomy have been discussed for a long time. In recent years, Yamashita et al.^[18] established a new side-overlap esophagogastrostomy to prevent reflux after proximal gastrectomy. Thus, the surgical techniques of reconstruction and patient QOL have been well discussed, and we can choose a moderate esophagogastrostomy reconstruction procedure based on several techniques according to their characteristics. However, objective data on esophagogastrostomy function have not yet been proven. Muraoka et al.^[4] described the "shutter mechanism" by using a hinged double flap under endoscopic observation. Spontaneous closure of the lower oesophagus was considered to be caused by the pressure between the oesophageal lumen and gastric lumen, leading to one-way valve function. Although the formation of a pseudo-fornix and a valve contributed to the logical explanation for the anti-reflux function, there are no reports of objective test data on the function of esophagogastrostomy with the hinged double flap method after proximal gastrectomy. Therefore, we assessed the function of esophagogastrostomy using the hinged double flap method by analyzing intraesophageal pressure.

In our study, we applied HRIM to evaluate the intraoesophageal pressure of esophagogastrostomy. Conventional oesophageal manometry uses recording sites every 5 cm in the oesophagus to measure the contraction and pressure. In contrast, HRIM obtains transducer probes, which are separated by only 1 cm in the oesophagus. The intraluminal pressure data from these transducers are converted into oesophageal motility data as a specific image in colour, known as oesophageal pressure topography^[19]. Compared to conventional oesophageal manometry, HRIM is the gold standard for diagnosing oesophageal motility disorders and is superior in terms of interpretative consistency and diagnostic accuracy^[20]. Consequently, HRIM is a method of observing oesophageal motility that provides the impetus for the new concept of the Chicago classification criteria for oesophageal motility disorders^[21].

Furthermore, the development of HRIM has made the postoperative assessment of patients' QOL possible after gastric surgery. Hoshino *et al.*^[22] also evaluated HRIM distal oesophageal HPZ and LES parameters in post-fundoplication patients.

Association between lower oesophageal sphincter pressure and subscale of the symptom domain of PGSAS-37								
	Integrated relax	ation pressure	LES resting	pressure	LES residual pressure			
	ρ	P*	ρ	P *	ρ	P *		
Oesophageal reflux subscale	- 0.5037	0.0199	- 0.3660	0.1027	- 0.4562	0.0377		
Abdominal pain subscale	- 0.3070	0.1758	- 0.0658	0.7767	- 0.2578	0.2592		
Meal-related distress subscale	0.0262	0.9102	- 0.0694	0.7649	- 0.1884	0.4134		
Indigestion subscale	- 0.3360	0.1365	- 0.1324	0.5673	- 0.3265	0.1486		
Diarrhoea subscale	- 0.3337	0.1393	- 0.2666	0.2427	- 0.4490	0.0412		
Constipation subscale	- 0.4029	0.0701	- 0.3037	0.1807	- 0.3721	0.0967		
Dumping subscale	- 0.0591	0.7990	0.0348	0.8809	- 0.0187	0.9358		
Total symptom score	- 0.3651	0.1037	- 0.2351	0.3050	- 0.3540	0.1154		

*Association between the three indices, integrated relaxation pressure, LES resting pressure, and LES residual pressure as an assessment of LES and each subscale of the symptom domain of PGSAS-37 (n = 16)

LES, lower oesophageal sphincter; PGSAS-37, Postgastrectomy Syndrome Assessment Scale-37.



Figure 3. The significant association between Postgastrectomy Syndrome Assessment. Scale-37 score and intraesophageal pressure "Oesophageal reflux subscale" was correlated with integrated relaxation pressure (A). "Oesophageal reflux subscale" was significantly lower in the abnormally high integrated relaxation pressure group (B). LES residual pressure was correlated with "Oesophageal reflux subscale" (C) and "Diarrhea subscale" (D). LES lower oesophageal sphincter. Normal integrated relaxation pressure group, high integrated relaxation pressure group.

They demonstrated that failed fundoplication possesses distinct HRIM patterns via different anatomical configurations. Herbella *et al.*^[23] showed normal oesophageal motility after total gastrectomy with Roux-en-Y reconstruction using HRIM. They also evaluated the presence of a postprandial proximal gastric acid pocket in patients receiving distal gastrectomy^[24]. Thus, evidence for HRIM in patients undergoing gastric surgery has been accumulating. However, reports referring to the dynamics and function of the LES postoperatively using HRIM have only been made with regard to fundoplication, total gastrectomy, or sleeve gastrectomy and not for esophagogastrostomy after proximal gastrectomy^[25]. This is the first study on intraesophageal pressure in patients receiving proximal gastrectomy with hinged double flap method using HRIM.

In the present study, the LES resting pressure created by the hinged double flap in patients was comparable to normal values in healthy participants, although all patients' LES residual pressure during swallowing-induced relaxation was abnormal postoperatively. In normal individuals, primary peristalsis appears in the upper oesophagus with swallowing, and relaxation of LES occurs at the same time. When the primary peristaltic wave reaches the LES, LES relaxation is completed. LES residual pressure, the pressure immediately after swallowing, was abnormally high in all patients, probably because the vagus nerve around the LES was resected, which did not produce sufficient swallowing-induced relaxation. On the other hand, IRP, the sum of pressures that occurs after LES residual pressure, normalized in some patients because of slow swallow-induced relaxation. Thus, while there was an abnormally high LES residual pressure and IRP values in certain patients after proximal gastrectomy, this was not necessarily a bad thing; rather, the high pressure worked to prevent oesophageal reflux. As previously described, esophagogastrostomy following proximal gastrectomy possess the possibility of reflux esophagitis as a disadvantage. Three different mechanisms of gastroesophageal reflux are generally accepted: transient complete relaxation of the LES, a transient increase in intra-abdominal pressure, or spontaneous free reflux associated with a low resting pressure of the LES^[26]. In patients after proximal gastrectomy, swallow-induced relaxation of the LES was considered a trigger for oesophageal reflux, and the lower the LES residual pressure and IRP values, even if normal, the more severe the reflux symptoms. It is possible that the required LES pressure is higher after proximal gastrectomy because of the relatively higher intragastric pressure due to the reduced volume of the remnant stomach.

The PGSAS-37 questionnaire was developed for the assessment of QOL in patients who underwent various types of gastrectomy. In recent years, the PGSAS-37 has been developed by the Japan Postgastrectomy Syndrome Working Party to establish an adequate instrument to assess the symptoms, living status, and QOL of postgastrectomy patients^[10,12]. Using this questionnaire, several nationwide multi-institutional collaborative studies have been conducted to elucidate the effects of gastrectomy procedures on the daily living of gastrectomized patients^[11-13,27-29]. Nakada et al.^[13] demonstrated that total gastrectomy with Roux-en-Y reconstruction and proximal gastrectomy among the six main gastrectomy procedures significantly impaired the QOL of postoperative patients. Therefore, it is essential to evaluate the function of the esophagogastric anastomosis and the QOL in patients who have undergone proximal gastrectomy, such as the one described in this paper. We objectively evaluated the function of the esophagogastric anastomosis in patients undergoing proximal gastrectomy with hinged double flap method and demonstrated for the first time that high residual LES pressure is involved in the anti-reflux mechanism.

Conclusions

This literature is notable that it is the first to objectively demonstrate the usefulness of the hinged double flap method using HRIM for patients undergoing proximal gastrectomy. The present study had some limitations, including the use of data generated from a single institution, retrospective design, and small sample size. However, our results provide supportive data for the availability of the hinged double flap method, and the use of HRIM, which was found to be useful in the evaluation of surgical techniques, will lead to the development of new surgical techniques in the future.

Ethical approval

This study was approved by the Institutional Review Board of Hiroshima University (No. E2019-1789-03), Hiroshima, Japan on 6 April 2023.

Consent

Ethics committee approval and fully informed written consent are obtained. Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

Author contribution

Y.S. designed and analyzed the data and wrote the paper; K.T., M.O., and E.T. edited the paper; E.C., H.O., R.I., Y.T., and N.K performed HRIM; H.O. supervised the project. All authors reviewed the manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

The research was registered in ResearchRegistry.com. The UIN is researchregistry 7951.

Guarantor

Hideki Ohdan.

Data availability statement

The data are available upon reasonable request.

Provenance and peer review

None.

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