

Aggressive Graphic/Surgical R0 Resection and Jejunal Interposition with Preservation of Mesojejunal Autonomic Nerves in Patients with Stage IV Esophagogastric Junction Adenocarcinoma: A Report of 3 Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest:

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None declared

Case series

Patients: Male, 54 • Male, 70 • Male, 59
Final Diagnosis: Esophagogastric junction adenocarcinoma
Symptoms: Epigastralgia
Medication: —
Clinical Procedure: Aggressive therapy
Specialty: Surgery

Objective: Unusual clinical course

Background: Three patients with stage IV esophagogastric junction cancer (EGJC) underwent extended resection to achieve a graphic/surgical R0 status (no visible remnant of viable tumor in imaging/surgical findings) and adjuvant chemotherapy from the early postoperative period. We also introduced use of our digestive reconstruction technique in these patients.

Case Report: We used jejunal interposition for digestive reconstruction, which involved end-to-end jejunojejunostomy with a biofragmentable anastomosis ring. The mesojejunal autonomic nerves of the lifted jejunum were preserved. The first adenocarcinoma involved the perilesional lymph nodes (LNs). Graphic/surgical R0 resection was completed by para-aortic LN dissection. The diagnosis (Japanese Classification of Gastric Carcinoma) was stage IV [pM1(LYM)]. Adjuvant chemotherapy began on postoperative day (POD) 11. The second adenocarcinoma was accompanied by a solitary lung metastasis. Intraoperative cytology of ascitic fluid was positive, and cisplatin was intraperitoneally administered. Adjuvant chemotherapy began on POD 10. The solitary lung metastasis was then resected, and graphic/surgical R0 resection was achieved. The diagnosis was stage IV [pM1(PUL) and CY1]. The third adenocarcinoma was accompanied by multiple liver metastases and metastatic regional LNs. The diagnosis was stage IV [H1]. Systemic chemotherapy was repeated. Only a solitary liver metastasis remained and was treated by radiofrequency ablation. Conversion surgery was conducted, achieving graphic/surgical R0 resection. Systemic chemotherapy was continued from POD 10.

Conclusions: For patients with stage IV EGJC, extended resection to achieve a graphic/surgical R0 status is still controversial, and systemic chemotherapy is important. The results of the present study suggest that our physiological reconstruction technique does not affect the efficacy of other therapies, such as adjuvant chemotherapy.

MeSH Keywords: Adenocarcinoma • Autonomic Pathways • Chemotherapy, Adjuvant • Drug Therapy • Esophagogastric Junction • Reconstructive Surgical Procedures

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Background

The incidence of esophagogastric junction adenocarcinoma has been increasing worldwide [1]. However, a standardized surgical strategy for treatment of esophagogastric junction cancer (EGJC) has not been established [1]. Although optimal lymph node (LN) dissection in the treatment of EGJC is still controversial, the hiatal LNs (No. 19 and 20) and lower mediastinal LNs (No. 110, 111, and 112) are the target LNs of intentional dissection in the 2018 Gastric Cancer Treatment Guidelines issued by the Japanese Gastric Cancer Association [2].

The clinical significance of extended resection to achieve a graphic/surgical R0 status according to the Japanese Classification of Gastric Carcinoma [3] and 2018 Gastric Cancer Treatment Guidelines [2] (i.e., no visible remnant of viable tumor in imaging and surgical findings) is also controversial. Highly motivated physicians and surgeons have a strong desire to improve the poor prognosis of advanced EGJC.

Oral intake and performance status may be disturbed after surgery [4]. Although adjuvant chemotherapy for selected patients with stage IV cancer is recommended [5–12], some physicians may have concerns about smooth introduction of such chemotherapy after surgery.

In our institution, we employed jejunal interposition for digestive reconstruction, in which end-to-end jejunojejunostomy was performed with a biofragmentable anastomosis ring [13]. Moreover, the mesojejunal autonomic nerves of the lifted jejunum were preserved [13,14]. We managed 3 patients with stage IV EGJC (adenocarcinoma) who underwent extended treatments for graphic/surgical R0 resection and adjuvant chemotherapy from the early postoperative period. Here, we report the details of our surgical procedures of digestive reconstruction for these patients with EGJC and present 3 thought-provoking cases with a literature review.

Case Report

Surgical procedures for digestive reconstruction

Intentional dissection of regional LNs (No. 1, 2, 3, 7, 8a, 9, 11p, 11d, 19, 20, 110, 111, and 112 according to the 2018 Gastric Cancer Treatment Guidelines [2]) was routinely performed. In our institution, the spleen and splenic LNs (No. 10, according to the Japanese Classification of Gastric Carcinoma [3]) were removed. Cholecystectomy was also routinely performed to prevent biliary complications due to postoperative vagal paralysis. Jejunal interposition was employed for reconstruction of the alimentary tract. Jejunojejunostomy was performed with a biofragmentable anastomosis ring in an end-to-end fashion.

The importance of preservation of mesojejunal autonomic nerves has been documented in the field of digestive surgery [15,16]. The interposing jejunum was harvested at a suitable point from the ligament of Treitz (Approximately 40 cm from the Treitz), and our surgical techniques for preservation of the mesojejunal autonomic nerves of the lifted jejunum are described in detailed elsewhere [13,14]. To preserve the physiological function of the autonomic nerves in the distal mesojejunum, the jejunum was sacrificed as close to the jejunal wall as possible (Figure 1A). Hence, the interposing jejunum could be lifted without even subtle tension on the lifted mesojejunum (Figure 1B); this provided better physiological conditions for the mesenteric autonomic nerves. Approximately 20 cm of the jejunum was sacrificed on the proximal side of the interposing jejunum, and approximately 10 cm was also sacrificed on the distal side (Figure 2). The interposing jejunum was lifted via the retrocolic route.

Anvil heads were fixed to the duodenal bulb and esophagus. Circular staplers were used to perform jejunoduodenostomy (EEA Circular Stapler with DST Series Technology, 25 mm, 4.8 mm; Medtronic plc, Dublin, Ireland) and esophagojejunostomy (EEA Circular Stapler with DST Series Technology, 21 mm, 4.8 mm; Medtronic plc). Esophageal anastomosis was performed in the mediastinal space, and interrupted seromuscular sutures were circumferentially placed. The jejunal stump was closed with a linear stapler, and interrupted seromuscular sutures were placed to cover the staple line.

Jejunojejunostomy was performed in an end-to-end anastomosis fashion with a biofragmentable anastomosis ring (Valtrac, 25 mm, 1.5 mm; Medtronic plc) (Figure 3A), and 4 interrupted seromuscular sutures were placed as retention sutures.

Case 1

The first case involved a 54-year-old man with inadequate oral intake and body weight loss. Diagnosis of advanced EGJC was made by endoscopic examination and imaging studies. Endoscopic biopsy revealed poorly differentiated adenocarcinoma, and the serum level of carbohydrate antigen 19-9 (188.7 U/ml) was elevated. He had no comorbidities, and his performance status was categorized as 0. Although distant metastasis was not detected in the imaging studies, the primary tumor might have involved perilesional LNs. The primary tumor extended into the esophagus (Figure 4A), and left thoracotomy was simultaneously performed (Figure 4B). The proximal margin of the thoracic esophagus was negative in rapid pathological examination. The regional LNs were completely dissected, and para-aortic LNs were also intentionally dissected. A graphic/surgical R0 status was achieved by extended resection with para-aortic LN dissection, and the patient's tumor marker level (33.5 U/ml) was normalized

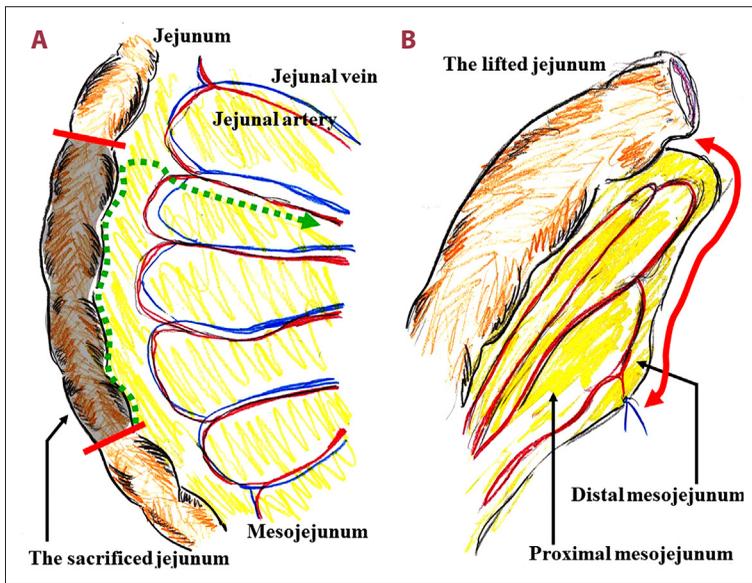


Figure 1. (A) To preserve the physiological function of the autonomic nerves in the distal mesojejunum, the resection line (green arrow) was set as close to the jejunal wall of the sacrificed jejunum (shaded area and red line) as possible. (B) The interposing jejunum could be lifted without even subtle tension on the lifted mesojejunum (red arrow).

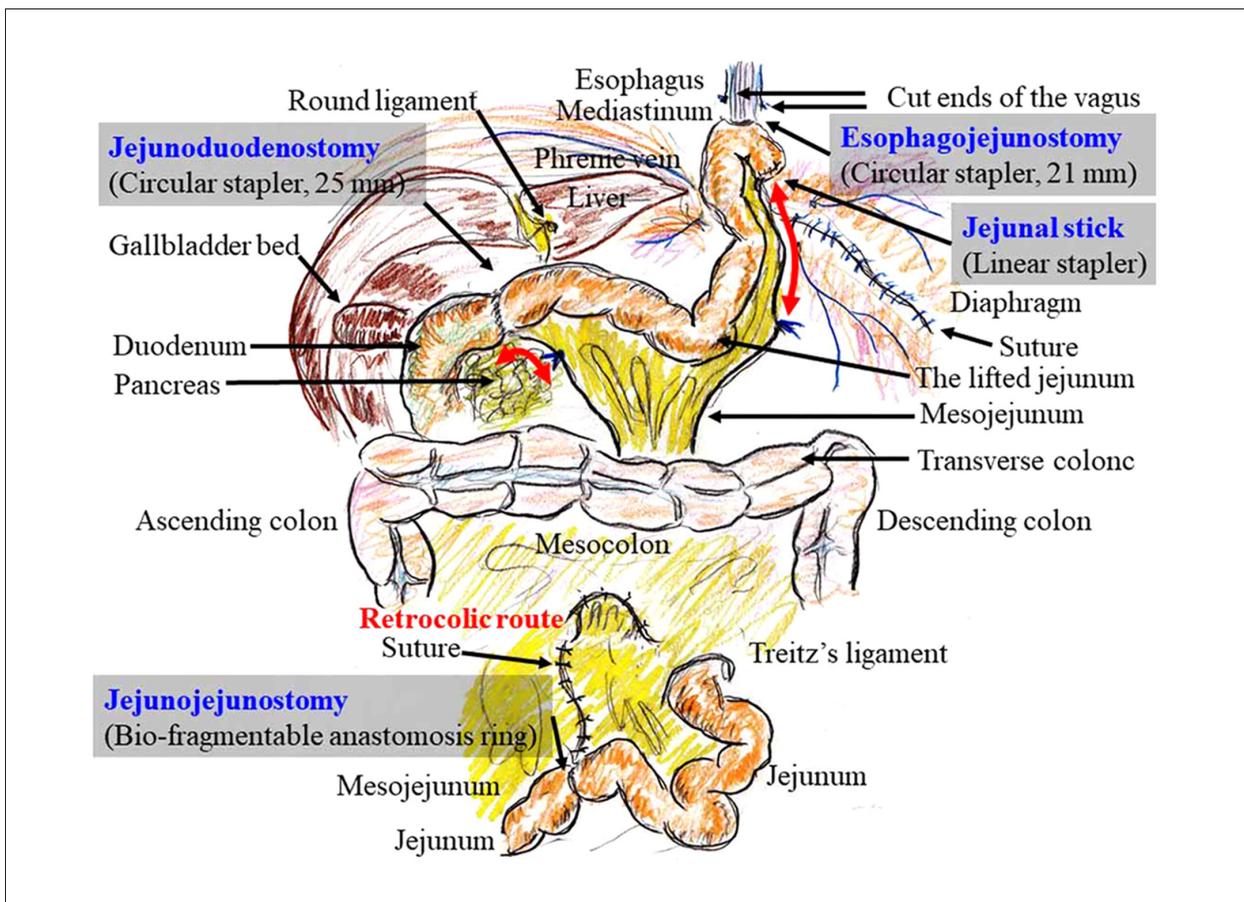


Figure 2. Approximately 20 cm of the jejunum was sacrificed on the proximal side of the interposing jejunum, and approximately 10 cm was sacrificed on the distal side (red arrows). The interposing jejunum was lifted via the retrocolic route. Jejunoduodenostomy (circular stapler, 25 mm) and esophagojejunostomy (circular stapler, 21 mm) were then performed. Esophageal anastomosis was performed in the mediastinal space, and the jejunal stump was closed with a linear stapler. Jejunojunctionostomy was performed in an end-to-end anastomosis fashion using a biofragmentable anastomosis ring.

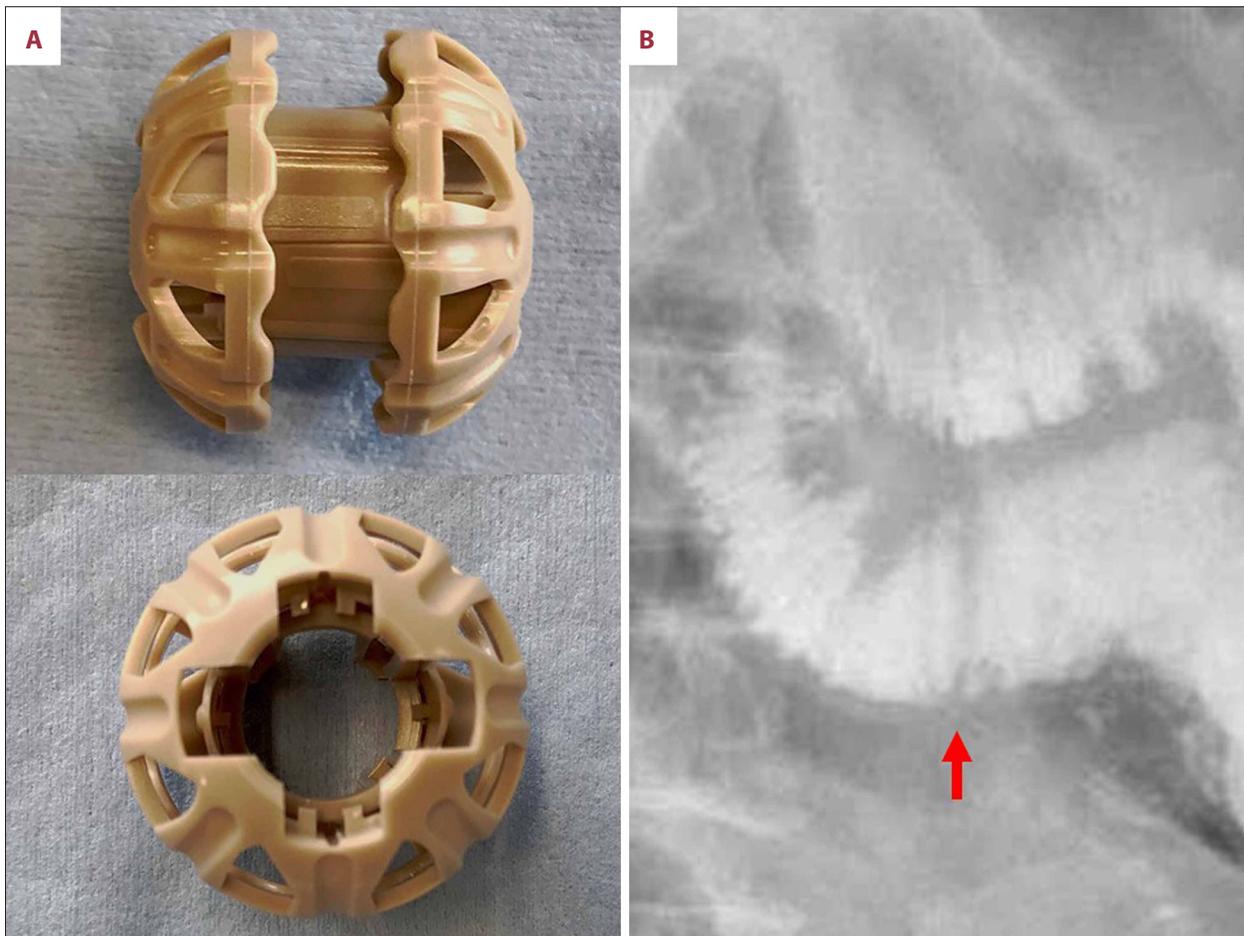


Figure 3. (A) Biofragmentable anastomosis ring (Valtrac, 25 mm, 1.5 mm; Medtronic plc) and dedicated forceps are currently available. (B) Actual finding of intestinal examination 3 months after surgery. The anastomotic point did not show a caliber change (red arrow).

immediately after surgery. The primary tumor seemed to involve the regional and para-aortic LNs (Figure 4C), and lymphoid metastasis was pathologically detected in one para-aortic LN. The definitive diagnosis based on the pathological findings of the resected specimens according to the Japanese Classification of Gastric Carcinoma [3] was pT3(SS) pN0 pM1(LYM) H0 P0 CY0 pStage IV. The postoperative course was uneventful. Adjuvant chemotherapy (S-1) began on postoperative day (POD) 11. No recurrence was detected 10 months after surgery.

Case 2

The second case involved a 70-year-old man with epigastric pain. A diagnosis of advanced EGJC was made by endoscopic examination (Figure 4D) and imaging studies. Endoscopic biopsy revealed moderately differentiated adenocarcinoma, and the serum level of carbohydrate antigen 19-9 was elevated. He also had hypertension and diabetes. His performance status was categorized as 0. A solitary lung metastasis was detected in imaging studies (Figure 5A). Although the proximal margin

of the thoracic esophagus was negative in rapid pathological examination, intraoperative cytology of ascitic fluid was positive (Figure 5B). Cisplatin was intraperitoneally administered during surgery. The definitive diagnosis based on pathological and imaging findings according to the Japanese Classification of Gastric Carcinoma [3] was pT4a(SE) pN1 cM1(PUL) H0 P0 CY1 pStage IV. The postoperative course was uneventful. Adjuvant chemotherapy (S-1) began on POD 10. Three months after surgery, the solitary lung metastasis showed no change, and no other distant metastases were detected. After a temporary stop of chemotherapy, the solitary lung metastasis was thoroscopically resected from the viewpoint of diagnostic therapy (i.e., rule out of primary lung cancer) at 4 months after the initial surgery, and the lung nodule was immunopathologically confirmed to be a metastatic tumor of EGJC. Graphic/surgical R0 resection was completed, and the tumor marker level was normalized immediately after lung resection. Thereafter, S-1 was resumed as adjuvant chemotherapy for 1 year after the initial chemotherapy. No recurrence was detected 14 months after the initial surgery.

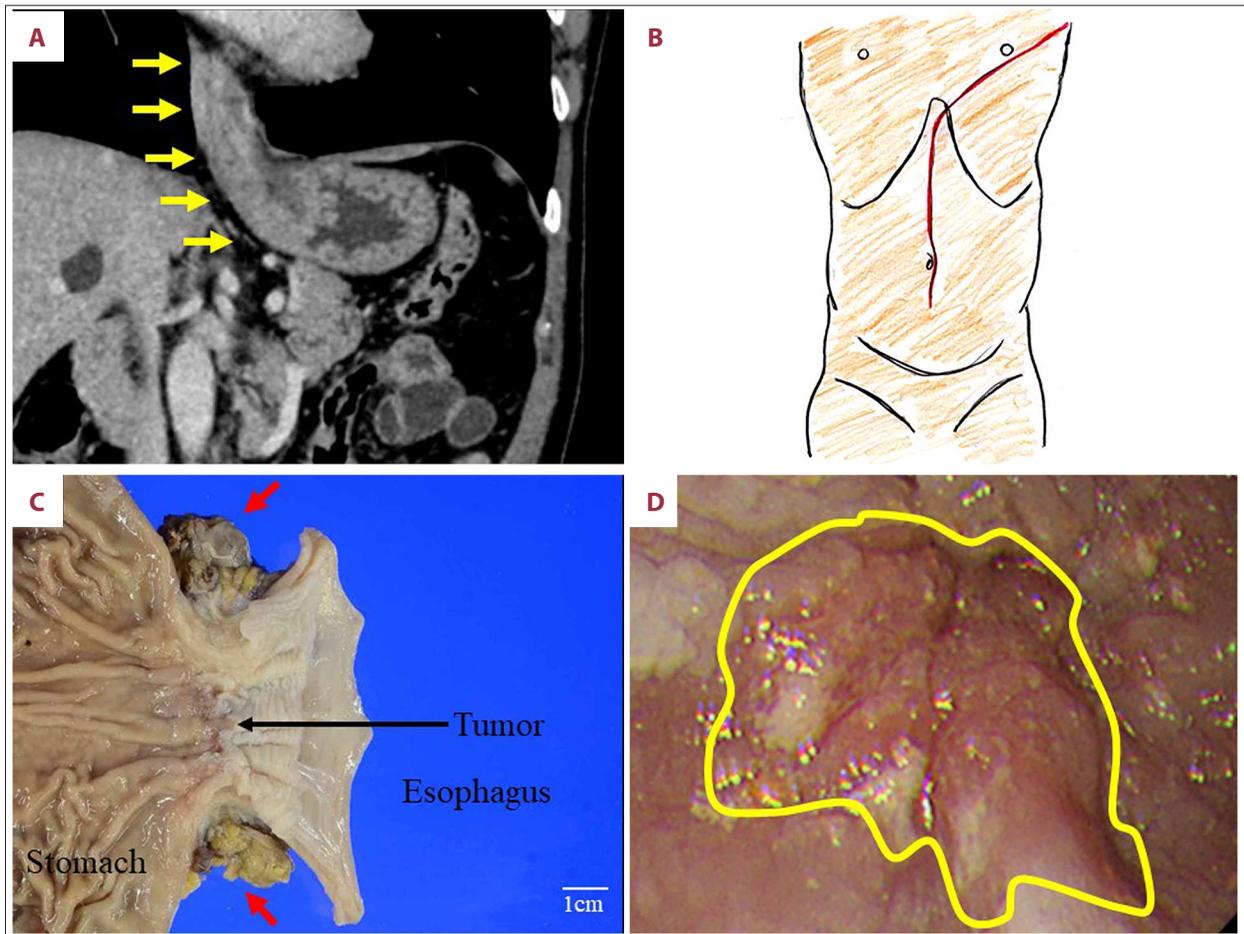


Figure 4. (A) The primary tumor extended into the esophagus (yellow arrows). (B) Left thoracotomy was simultaneously performed. (C) The primary tumor appeared to involve the regional and para-aortic lymph nodes (red arrows). (D) Endoscopic findings revealed advanced esophagogastric junction cancer (yellow area).

Case 3

The third case involved an asymptomatic 59-year-old man with no comorbidities. Tumor marker screening during his health check revealed a significantly elevated level of carcinoembryonic antigen. Endoscopic examination and imaging studies revealed advanced EGJC. Endoscopic biopsy revealed moderately differentiated adenocarcinoma, and human epidermal growth factor receptor 2 was negative. His performance status was categorized as 0. Multiple liver metastases (Figure 5C) and metastatic regional LNs were detected in imaging studies, including positron emission tomography/computed tomography. The clinical stage according to the Japanese Classification of Gastric Carcinoma [3] was cT3(SS) cN2 M0 H1 P0 CYX cStage IV. Three courses of systemic chemotherapy of S-1 plus oxaliplatin were completed with adverse effects (platelet depletion and edematous bowels), and imaging studies revealed that the swelling of the regional LNs had completely disappeared and that the multiple liver metastases were drastically down-regulated. Only a solitary liver metastasis remained, and the size of this persistent

metastasis was reduced. Radiofrequency ablation (RFA) was performed for the remaining solitary metastasis (Figure 5D). The tumor marker level was drastically normalized after chemotherapy and RFA. Hence, conversion surgery was conducted to achieve a graphic/surgical R0 status. Both the proximal margin of the thoracic esophagus in rapid pathological examination and the intraoperative cytological examination of ascitic fluid were negative. The pathological diagnosis according to the Japanese Classification of Gastric Carcinoma [3] was ypT3 ypN1. The postoperative course was uneventful, and systemic chemotherapy of S-1 plus oxaliplatin was continued from POD 10. No recurrence was detected 12 months after surgery.

Discussion

The Murphy button was introduced by JB Murphy in 1892 [17] and was a major breakthrough in the field of intestinal surgery [17,18]. The biofragmentable anastomosis ring and dedicated forceps are currently available and are based on

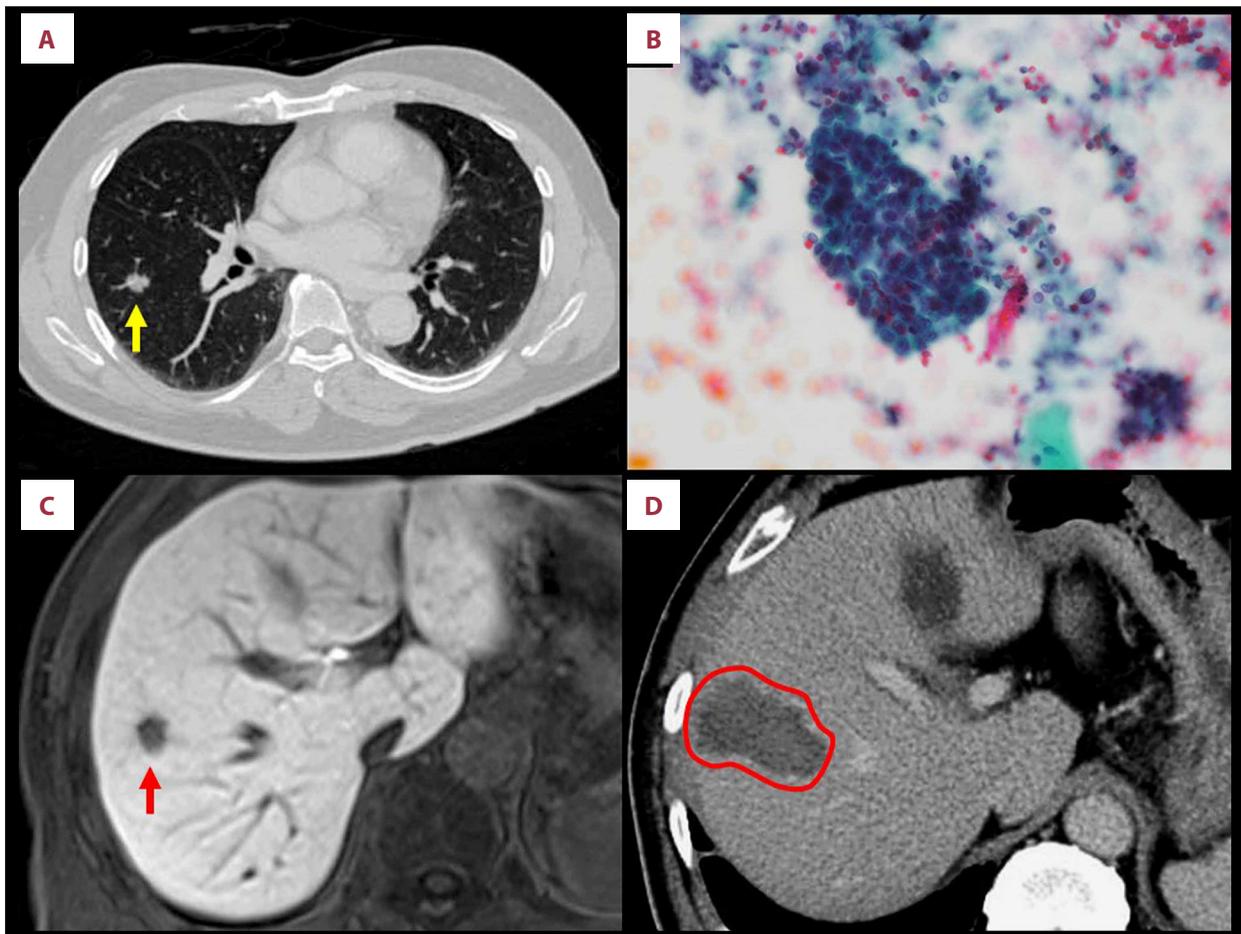


Figure 5. (A) A solitary lung metastasis was detected (yellow arrow). (B) Intraoperative cytological examination of ascitic fluid was positive (Papanicolaou stain). (C) Multiple liver metastases were detected by magnetic resonance imaging with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (red arrow). (D) The down-regulated solitary liver metastasis was treated by radiofrequency ablation (red area).

the concept of the Murphy button [17]. The biofragmentable ring (Valtrac, 25 mm, 1.5 mm; Medtronic plc) will break into pieces within 3 weeks, and we have a clear impression that jejunojejunostomy performed in an end-to-end fashion with a biofragmentable ring does not cause a postoperative passage obstruction. End-to-end anastomosis may not be easily detected in the postoperative examination because the anastomotic point does not show a caliber change. The actual finding of the intestinal examination at 3 months postoperatively is shown in Figure 3B.

Gastrectomy with D2 LN dissection is the standard treatment for curable gastric cancer [2]. The addition of para-aortic LN dissection does not improve the survival rate in patients with curable gastric cancer [19]. A Japanese nationwide prospective trial was conducted to determine the proportion of LN metastasis in esophagogastric cancers and identify the optimal extent of LN dissection in each type [1]. Metastasis to LNs other than regional LNs is defined as distant metastasis

in EGJC [3], although the para-aortic LNs in upper gastric cancer were historically considered regional LNs in the previous Japanese Classification of Gastric Carcinoma. Para-aortic LN dissection offers marginal therapeutic value in patients with stage IV EGJC [20] and depends on the subtype of EGJC [21]. In selected patients who undergo neoadjuvant chemotherapy, intentional dissection of the para-aortic LNs may be effective if para-aortic LN metastasis is not massive [22,23].

The hiatal LNs (No. 19 and 20) and lower mediastinal LNs (No. 110, 111, and 112) are target LNs of intentional dissection for EGJC [24–29]. The left thoracoabdominal approach and abdominal-transhiatal approach to LN dissection have been compared [24]. The abdominal-transhiatal approach is recommended if the tumor size is <4 cm or the proximal side of the tumor is ≤ 3 cm from the esophagogastric junction [2,24]. In *Case 1*, we employed the left thoracoabdominal approach for intentional dissection of the para-aortic LNs to achieve

Table 1. Clinical profiles.

Case	1	2	3
Age	57,1	70,3	59
Gender	Male	Male	Male
Comorbidity	None	Diabetes	None
Performance status	0	0	0
Stage*	IV	IV	IV
Distant metastasis	Paraaortic lymph node	Ascites, lung	Liver
Neoadjuvant chemotherapy	No	No	Yes
Operative time (minute)	288	247	285
Blood loss (ml)	538	505	460
Additional therapy	Extended lymph node dissection	Intraperitoneal administration, lung resection	Liver RFA
Graphic R0**	Yes	Yes	Yes
Surgical R0**	Yes	Yes	Yes
Start of meal intake (POD)	5	4	6
Adjuvant chemotherapy	Yes	Yes	Yes
Start of adjuvant chemotherapy (POD)	11	10	11
Postoperative hospital stay (day)	12	12	12
Follow-up term (month)	10	14	12
Recurrence	Not detected	Not detected	Not detected
Tumor marker	Normalized	Normalized	Normalized
Prognosis	Alive	Alive	Alive

* Japanese Classification of Gastric Carcinoma; **: Japanese Classification of Gastric Carcinoma and Gastric Cancer Treatment Guidelines 2018. POD – postoperative day.

surgical curability because the preoperative imaging findings suggested that the LNs near the EGJC might be metastatic.

The effectiveness of intraperitoneal administration of paclitaxel or cisplatin has been documented [30–32]. In our institution, cisplatin is intraperitoneally administrated for patients with positive cytologic examination of ascitic fluid and no visible dissemination nodules (P0 CY1 according to the Japanese Classification of Gastric Carcinoma [3]). Only in *Case 2*, cisplatin was intraperitoneally administrated during surgery.

In the field of gastric cancer, hepatectomy for liver metastases may be acceptable if the patient has a small number of metastases and no factors indicating unresectability [33–35]. The usefulness of RFA has been documented for liver metastasis of colorectal cancer [36–39], and RFA may be an alternative

to hepatectomy in patients with gastric cancer [40–43]. RFA seemed to be effective in our patient (*Case 3*).

In the field of EGJC, the effects of chemotherapy alone versus chemotherapy followed by surgical resection have been investigated [44]. We understand that whether aggressive treatment should be performed to achieve a graphic/surgical R0 status (e.g., extended resection and RFA) is still controversial. Although the number of patients was low and the follow-up duration was relatively short in the present report, both aggressive treatments to achieve a graphic/surgical R0 status and systemic chemotherapy after surgery seemed to well work for our patients with stage IV EGJC. Postoperative adjuvant chemotherapy is generally recommended for patients with stage IV cancer exhibiting positive ascites cytology (CY1) [5–8] and a surgical R0 status [6,9–12]. The clinical profiles of our

3 patients are summarized in Table 1; note that all patients received adjuvant chemotherapy from the early postoperative period (POD 10 or 11). Sufficient oral intake is important for excellent postoperative course [13,14,44,45]. Adequate intakes in each case were accomplished at each POD of start of meal intake, if adequate intake was defined as a dietary intake of more than half of meal [13,14,45]. Systemic chemotherapy is a key in the treatment of stage IV EGJC [20,46]. From the viewpoint of physiological postoperative function, jejunal interposition reconstruction with preservation of the mesojejunal autonomic nerves may play an important role in guaranteeing adequate oral intake and avoiding any disturbances of adjuvant chemotherapy in patients with stage IV EGJC. In our opinion, clinical decision-making regarding the timing of surgery is difficult. Our experience and follow-up term were insufficient to judge the disease process and to verify the validity of our management, and more studies are urgently needed.

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Conclusions

The alimentary tract should be reconstructed once surgical graphic/surgical R0 resection is chosen. Physiological reconstruction by jejunal interposition with preservation of the mesojejunal autonomic nerves may be a key to avoiding any disturbances of the efficacy of other therapies, including adjuvant chemotherapy, in patients with stage IV EGJC. We hope our experiences will be informative in the field of advanced EGJC.

Acknowledgments

Tomohide Hori created original drawings of all schemas.

Conflict of interest

None.

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