Table 2. Results of Univariate Analyses Using the Log-Rank Test to Identify Prognostic Factors

		Survival Rate (%)			
	n	1 Year	2 Year	3 Year	*P*
All patients	21	85.7	54.8	38.4	
Age					.91
≥ 65 y	15	80.0	53.3	33.3	
< 65 y	6	80.0	53.3	53.3	
Disease-free interval					.91
≥ 1 y	6	83.3	50.0	33.3	
< 1 y	15	86.7	56.9	40.6	
Time to pulmonary metastases from primary therapy					
≥ 1 y	7	85.7	57.1	42.9	.6
< 1 y	14	85.7	53.4	35.6	
Number of pulmonary metastases at the time of initial RF ablation sessions					.94
Single	14	85.7	54.5	31.2	
Multiple	7	85.7	53.6	53.6	
Largest size of ablated tumors					.71
≥ 2 cm	10	90.0	50.0	40.0	
< 2 cm	11	81.8	62.3	37.4	
History of extrapulmonary recurrences					.21
Yes	9	77.8	33.3	22.2	
No	12	91.7	72.2	51.6	
Viable extrapulmonary recurrences at the time of initial RF ablation sessions					< .001
Yes	3	33.3	0.0	0.0	
No	18	94.4	64.2	44.9	
Chemotherapy before RF ablation					.79
Yes	8	87.5	31.3	31.3	
No	13	84.6	68.4	42.7	
Chemotherapy after RF ablation*					.15
Yes	15	93.3	63.8	47.9	
No	5	80.0	40.0	20.0	

RF = radiofrequency.
*A missing datum was excluded from the analysis.

Table 3. Adverse Events after 27 Procedures

Grade*	Adverse Events	n	%
1	Pneumothorax without symptoms	8	29.6
	Pleural effusion without symptoms	7	25.9
	Hemothorax	2	7.4
2	Pneumothorax requiring chest tube placement	2	7.4
	Pneumoderma requiring chest tube placement	1	3.7
	BOOP-like reactive pneumonitis	1	3.7
3	Pneumoderma requiring surgical intervention	1	3.7
	Pleural effusion requiring chest tube placement	1	3.7

BOOP = bronchiolitis obliterans organizing pneumonia.
*Categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

or stereotactic radiation therapy. However, generally, large tumors are likely to be treated with stereotactic radiation because of the limited local efficacy of RF ablation on such tumors. RF ablation is preferable when stereotactic radiation appears hazardous (eg, when a tumor is located near the hilum, mediastinum, lung apex, or vertebral body). In addition, RF ablation tends to be indicated in patients with severe pulmonary dysfunction because stereotactic radiation is considered to be more toxic (mainly because of radiation pneumonitis). When both therapies are feasible, treatment selection depends on the physician's preference.

The presence of viable extrapulmonary recurrence at the time of the initial RF ablation session was a significant prognostic factor in the present study population. Similarly, a previous study of metastasectomy showed that antecedent extrapulmonary metastasis was an unfavorable prognostic factor (7). Previous studies of RF ablation for lung metastases from colorectal cancer also showed that extrapulmonary metastasis is an independent prognostic factor (16,19,20). Based on these results, patients without extrapulmonary recurrences appear to be more suitable candidates for lung RF ablation.

The present study suggests that RF ablation is a safe procedure for pulmonary metastases from esophageal cancer; grade 3 adverse events were observed in 7.4% of

cases, and no grade 4 or higher events were observed. Pneumothorax was the most common complication after lung RF ablation. The incidence of pneumothorax after chest tube placement in the present study population was similar to the incidence reported in previous studies (31).

This study has several limitations. The study was retrospective and included a relatively small study population. Histologic confirmations of pulmonary metastases were not always obtained. The treatment strategies were heterogeneous, including various combinations with other modalities, such as chemotherapy, radiation therapy, and surgery. The follow-up period was too short to investigate long-term outcomes. In addition, this study did not include a control group and could not assess any survival benefit conferred by RF ablation compared with no treatment or with any specific therapy.

In conclusion, the survival outcomes after RF ablation in the present study population were promising, and this new local therapy may be a useful additional treatment option for patients with pulmonary metastases from esophageal cancer. A prospective study with a larger study population is needed to determine the long-term outcomes of this treatment option.

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REVIEW

Molecular diagnosis and therapy for occult peritoneal metastasis in gastric cancer patients

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Abstract

To apply an individualized oncological approach to gastric cancer patients, the accurate diagnosis of disease entities is required. Peritoneal metastasis is the most frequent mode of metastasis in gastric cancer, and the tumor-node-metastasis classification includes cytological detection of intraperitoneal cancer cells as part of the staging process, denoting metastatic disease. The accuracy of cytological diagnosis leaves room for improvement; therefore, highly sensitive molecular diagnostics, such as an enzyme immunoassay, reverse transcription polymerase chain reaction, and virus-guided imaging, have been developed to detect minute cancer cells in the peritoneal cavity. Molecular targeting therapy has also been spun off from basic research in the past decade. Although conventional cytology is still the mainstay, novel approaches could serve as practical complementary diagnostics to cytology in near future.

Key words: Gastric cancer; Peritoneal lavage; Cytology; Molecular diagnostic techniques; Reverse transcriptase polymerase chain reaction; Carcinoembryonic antigen

Core tip: For patients with gastric cancer, cytological detection of cancer cells in the peritoneal cavity is important to predict future manifestation of peritoneal recurrence. However, its improvement has been a matter of research, because of its low sensitivity and specificity. The new diagnostic modalities have been investigated along with the development of modern molecular biology. The recent innovative challenges regarding molecular diagnosis of intra-peritoneal gastric cancer cells have been thoroughly covered and summarized. The new therapies for gastric cancer with peritoneal spreads were also referred.

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INTRODUCTION

Gastric cancer is one the leading causes of death in the world[1], and the most prevalent cancer in Eastern Asia[2]. Although the radical resection of cancerous lesions is the only cure for gastric cancer, multi-disciplinary therapy

for advanced disease can palliate the disease and even prolong life[3,4]. Therefore, the accurate and appropriate diagnosis of the disease entity is required so that an individualized oncological approach can be used. The tumor-node-metastasis (TNM) staging system is the universally accepted method to describe the degree of cancer advancement[5,6]. As with other cancers, gastric cancer has disease-specific factors in its staging. One of them is the cytology of a peritoneal wash or ascites because peritoneal metastasis is the most frequent mode of distant metastasis and post-surgical recurrence. However, it is often difficult to diagnose peritoneal metastasis by conventional imaging modalities, such as computed tomography and positron emission tomography. The cytological detection of free cancer cells in the peritoneal cavity is a very important finding in gastric cancer. Positive cytology means that peritoneal metastasis exists anywhere in the peritoneal cavity even if it is invisible, so it implies a high probability of future manifestations of peritoneal metastasis[7-12]. Therefore, peritoneal lavage cytology findings as well as peritoneal metastasis are factors in gastric cancer staging in Japan as stage 4 disease[13]. The most recent TNM classification system includes intraperitoneal cancer cell detection as part of the staging process, denoting metastatic disease[5].

Peritoneal carcinomatosis is an incurable disease with poor prognosis. In cases of peritoneal carcinomatosis, although debate about surgical application still remains, palliative chemotherapy would be preferred[14-17]. From this point of view, peritoneal carcinomatosis needs to be precisely diagnosed before surgery or at the beginning of surgery for surgeons to determine the most appropriate therapeutic approach[18]. However, in reality, the uneven shape of the peritoneal cavity makes it impossible for the entire cavity to be thoroughly inspected and difficult for the surgeon to definitively judge whether the peritoneal cavity is completely free of metastatic foci. Consequently, peritoneal lavage cytology is needed for the indirect diagnosis or prediction of peritoneal metastasis, and it must be as accurate as possible. The accuracy in peritoneal lavage cytology depends greatly upon the experience of the cytopathologist; therefore, the diagnosis remains inevitably subjective. In addition, several studies indicate that the sensitivity and specificity of peritoneal lavage cytology is unsatisfactory and that there is still room for improvement[19]. Over the past decade, several new diagnostic approaches have been studied. As an alternative to conventional cytology by Papanicolaou staining, immunocytochemistry or PCR-based genetic detection of epithelial or malignant cells in the peritoneal fluid has emerged (Table 1). There are advantages and shortcomings of each approach[20]. In this review, we examine recent studies, summarize findings on the molecular biology-based diagnosis of peritoneal cancer cell existence, and discuss recent advances in the treatment of peritoneal carcinomatosis.

CONVENTIONAL CYTOLOGY

Since the method of lavage cytology was described by Moore *et al*[21] in 1961, several clinical studies have demonstrated the prognostic significance of intraperitoneal free cancer cells at the time of surgery[7,10,12,16,17,22-25]. The Japanese Classification of Gastric Carcinoma (2nd English edition) first included the result of peritoneal cytology as one of the staging parameters in 1999[26]; since then, the Japanese Gastric Cancer Association includes peritoneal cytology in their staging system[14]. Although the most recent TNM classification has included the detection of intraperitoneal free cancer cells as part of the staging process, denoting M1 disease[5], the application of peritoneal cytology in preoperative staging is still controversial. The European Society for Medical Oncology practice guidelines recommend laparoscopy, but regard cytology as optional, and the current National Comprehensive Cancer Network (NCCN) guidelines also do not include cytology in the treatment algorithm[27]. Nevertheless, peritoneal cytology has important clinical implications in the management of advanced gastric cancer[7,28].

In gastric cancer surgery, by either laparotomy or laparoscopic approach, about 100-200 mL of saline is usually instilled into the Douglas pouch (and occasionally into the left subphrenic space) and gently stirred. A washing sample is then aspirated and subjected to cytology. Traditionally, Papanicolaou or Giemsa stainings are employed, and specimens are diagnosed by experienced cytopathologists. The accuracy, sensitivity, and specificity of conventional cytology in predicting peritoneal recurrence was 73.0%-91.9%, 11.1%-80.0%, and 86.4%-100.0%, respectively[20]. Thus, sensitivity had a particularly wide range, which indicated the need for further advanced techniques.

CARCINOEMBRYONIC ANTIGEN IN PERITONEAL LAVAGE

Kanetaka *et al*[29] recently reported that the measurement of carcinoembryonic antigen (CEA) level in peritoneal lavage (pCEA) by an enzyme immunoassay can predict poor prognosis and may help to elucidate a cohort who need more intensive adjuvant chemotherapy to improve their prognosis. Since Asao *et al*[30] first reported that the CEA antigen level in peritoneal lavage could reflect the presence of peritoneal metastasis more accurately than conventional cytology in 1991, other investigators have demonstrated the clinical significance of pCEA levels[31-35]. Most of these reports showed a significant correlation between pCEA level and survival after surgery, implying that pCEA could be a potential predictor of poor prognosis. However, the pCEA level may reflect both the production of CEA in the peritoneal cavity and the serum CEA level and may not be specific as a marker for the existence of intraperitoneal free cancer cells or occult peritoneal metastasis.

Table 1 List of published studies regarding the molecular diagnosis of peritoneal fluid in gastric cancer

Ref.	Molecule	Technique	Number of patients	Results
Asao *et al*[30]	CEA	Enzyme immunoassay	120	Correlation with 2-yr survival rate
Irinoda *et al*[32]	CEA, sialyl-Tn antigen	Enzyme immunoassay	96	Correlation with peritoneal metastasis and prognosis
Abe *et al*[31]	CEA	Enzyme immunoassay	56	Correlation with peritoneal metastasis and overall survival
Cetin *et al*[34]	CEA	Enzyme immunoassay	70	Correlation with peritoneal metastasis and overall survival
Kanetaka *et al*[29]	CEA	Enzyme immunoassay	597	Correlation with overall survival and peritoneal recurrence free survival
Yamamoto *et al*[33]	CEA, CA125	Enzyme immunoassay	229	Correlation with overall survival and recurrent cites
Li *et al*[35]	CEA	Radioimmunoassay	64	Correlation with overall survival
Kodera *et al*[38]	CEA	RT-PCR	189	Correlation with overall survival and peritoneal recurrence-free survival
Wang *et al*[36]	CEA	RT-PCR	40	Correlation with peritoneal recurrence
Sugita *et al*[41]	CEA, CK20	RT-PCR	129	Correlation with overall survival and peritoneal recurrence-free survival
Dalal *et al*[37]	CEA, CK20, survivin, MUC2	RT-PCR	40	CEA had high sensitivity and specificity, while CK20, survivin, and MUC2 showed high false-positive rates
Takata *et al*[42]	CEA, CK20	RT-PCR	104	Predict peritoneal recurrence
Kodera *et al*[40]	CK20	RT-PCR	195	Not sufficiently sensitive as CEA
Yonemura *et al*[39]	MMP-7	RT-PCR	152	Improved the sensitivity for peritoneal dissemination in combination with cytology
Mori *et al*[43]	Multiple marker	Microarray	179	Correlation with disease-free survival and immuno-cytochemical cytology
Hiraki *et al*[52]	Aberrant gene methylation	Methylation-specific PCR	107	Correlation between positive methylation and peritoneal recurrence
Mori *et al*[56]	Telomerase activity	TRAP assay	46	Some concordance with cytology
Da *et al*[57]	Telomerase activity	TRAP assay	60	Correlation with high proliferating activity of gastric cancer
Wong *et al*[62]	Viral tropism	NDV-GFP imaging	30	Higher sensitivity and lower specificity than cytology
Kitayama *et al*[58]	EpCAM	Flow cytometry	195	Tumor cell/leukocyte ratio reflects peritoneal spread

CEA: Carcino-embryonic antigen; CA125: Cancer antigen 125; CK20: Cytokeratin 20; TRAP assay: Telomeric repeat amplification protocol assay; NDV-GFP: Newcastle disease virus-green fluorescent protein; MUC2: Mucin 2; RT-PCR: Reverse transcription polymerase chain reaction.

GENETIC DETECTION OF INTRAPERITONEAL GASTRIC CANCER CELLS

Molecular diagnosis with reverse transcriptase-polymerase chain reaction (RT-PCR) has been employed for the detection of minimal cancer cells due to its high sensitivity. Among the messenger RNA (mRNA) specific to cancer cells or epithelial cells, the most common target molecule is CEA mRNA. PCR evaluation of CEA mRNA in peritoneal fluid has increased sensitivity for the detection of peritoneal cancer cells as compared to cytology[36,37], and positive results have been associated with poor survival. Kodera *et al*[38] demonstrated that CEA PCR-positive patients had significantly worse overall survival and recurrence-free survival as compared to PCR-negative patients, independently of cytology. PCR appears to increase the accuracy of detection of occult disease.

In addition, molecular targets for PCR other than CEA have been investigated and include metalloprotease-7[39] and cytokeratin 20[40,41]. The expression level of a single gene was heterogeneous, so limited sensitivity hinders its use alone. To further improve the sensitivity and specificity of the mRNA detection approach, multiplex PCR may prove to be more clinically useful in capturing intraperitoneal free cancer cells[41-43].

Mori *et al*[44] tried to select marker candidates out of tens of thousands of genes with microarray analysis, and they identified the genes specific to cytology-positive samples. They further manufactured a microarray chip containing 10 marker genes as a "MiniChip" and demonstrated that the MiniChip assay has a sensitivity and specificity equal to or better than conventional cytology in detecting minimal free cancer cells in peritoneal fluid[43].

Recently, a new rapid genetic diagnostic technique to detect minute cancer cells has been developed and applied in the sentinel node navigation surgery as surgical decision making[45-48]. One-step nucleic acid amplification (OSNA) uses reverse transcription loop-mediated isothermal amplification (RT-LAMP) to detect mRNA expression of target sequences from crude samples without RNA purification[49]. The reaction can be completed in a single test tube and within 1 h. Kumagai *et al*[50] reported a multicenter study evaluating the clinical performance of the OSNA assay that detects cytokeratin 19 (CK19) mRNA in detecting lymph node (LN) metastases in gastric cancer patients, and this method showed high concordance rate to pathology. Although the OSNA assay is useful in the intraoperative rapid diagnosis of LN metastasis for gastric cancer, it remains unproven if this technique could be ap-

plied to detect intra-peritoneal free cancer cells. It needs to be determined how the different properties of cells in the peritoneal cavity interfere with the reaction and what the minimal number of cancer cells is for detection by this method.

DNA methylation is an important epigenetic change in cancer that leads to the recruitment of transcription repressors and chromatin changes, so methylation analysis has been used as a diagnostic modality for various cancers[51]. Hiraki *et al*[52,53] assessed whether gene methylation in peritoneal fluid from gastric cancer patients is clinically feasible for determining the peritoneal metastasis in gastric cancer. By using quantitative methylation-specific PCR to compare aberrant methylation status in gastric cancer, they isolated 6 genes (*BNIP3*, *CHFR*, *CYP1B1*, *MINT25*, *RASSF2* and *SFRP2*) as having cancer-specific DNA methylation, and they observed that there was a significant correlation between positive methylation in any of these 6 genes and peritoneal recurrence[52]. Thus, methylation analysis might improve the positive detection of gastric cancer cells in peritoneal lavage.

TELOMERASE ACTIVITY IN THE PERITONEAL FLUID

Telomerase activity in cancer cells has been examined as a tag to detect cancer cells in the peritoneal cavity. Telomerase activity is one of the hallmarks of cancer and can be used to discriminate malignant cells from normal ones[54,55]. Mori *et al*[56] analyzed peritoneal lavage fluid employing a TRAP assay that reflects telomerase activity. To improve the efficacy of the assay, they enriched cancer cells with immunomagnetic beads coated with anti-Ber-EP4 antibody. Then, they successfully detected telomerase activity in the samples from gastric cancer patients with serosal or subserosal invasions, and they found some concordance with the results of cytology[56]. Da *et al*[57] have also investigated the telomerase activity in peritoneal lavage from gastric cancer patients without enrichment of cancer cells. Although the sample size was relatively small, their data demonstrated that all patients with peritoneal metastasis had detectable telomerase activity in peritoneal lavage fluid, and they found significant correlations between positive rate of telomerase activity and invasion depth, serosa-involved areas, and the presence and extent of peritoneal metastasis. While these methods were unique and appeared to be sensitive, they were not significantly superior to conventional cytology by itself. Nevertheless, telomerase activity analysis in peritoneal lavage fluid might be a helpful adjunct for the cytology in the diagnosis of occult peritoneal metastasis of gastric cancer.

FLOW CYTOMETRIC ANALYSIS OF FREE CANCER CELLS IN PERITONEAL LAVAGE FLUID

Kitayama *et al*[58] tried to quantify the free cancer cells recovered from ascites or peritoneal lavage fluid from gastric cancer patients by conventional flow cytometry. The peritoneal lavage fluid from gastric cancer patients contains erythrocytes, leukocytes, dissociated peritoneal mesothelium, and a small number of cancer cells. Therefore, molecular detection needs to distinguish cancer cells from normal cells co-existing in the peritoneal cavity. Kitayama *et al*[58] stained the cells with monoclonal antibodies to CD45 and CD326 (EpCAM), and CD326-positive and CD45-positive cells were classified as either cancer cell or leukocytes. Instead of using the total number of cancer cells, they calculated the cancer cell/leukocyte ratio and demonstrated that the ratio was significantly higher in the patients with peritoneal metastasis and positive cytology than in those without peritoneal spread. They further showed the ratio to reflect well the effect of intraperitoneal chemotherapy. They thus proposed that the flow cytometry-based measurement of the intraperitoneal CD326(+)/CD45(+) ratio could be a diagnostic marker that reflects the severity of peritoneal metastasis as well as the effectiveness of intraperitoneal chemotherapy.

Besides gastric cancer, ovarian cancer also often forms excess ascites due to peritoneal metastasis, which is routinely drained and discarded for symptomatic relief. Peterson *et al*[59] regard the ascites as a source of cancer cells for monitoring the treatment response of ovarian cancer. Miniaturizing and advancing flow cytometric technology, they developed and tested a new microfluidic chip to capture, enrich and analyze ascites tumor cells in ovarian cancer patients. This technology allows the detection of occult cancer cells and enables the molecular profiling of individual cells. The microfluidic chip might be applicable to the diagnostic and molecular analysis of peritoneal fluid from gastric cancer patients.

DIAGNOSTIC POTENTIAL OF THE VISUAL DETECTION OF CANCER CELLS IN PERITONEAL CYTOLOGY SAMPLES

As a unique approach, several groups examined virus-mediated fluorescent gene expression to visually detect rare cancer cells in the body fluid or the cytology samples against millions of normal cells[55,60,61]. Wong *et al*[62] evaluated a novel detection technique for intraperitoneal free cancer cells by using Newcastle disease virus-green fluorescent protein (NDV-GFP), which is genetically modified NDV that expresses the green fluorescent protein gene. Newcastle disease virus has been studied since the 1950s for its ability to infect and replicate specifically in tumors. NDV-GFP targets and infects specifically cancer cells, resulting in specific GFP expression. Wong *et al*[62] evaluated peritoneal lavage samples from 30 gastric cancer patients undergoing staging laparoscopy with NDV-GFP. They found that NDV-GFP-mediated detection offers a more sensitive method of identifying free peritoneal gastric cancer cells in peritoneal lavage fluid as compared to conventional Pap staining cytology to dem-

onstrate that NDV-GFP could be used diagnostically.

WHAT IS NEXT FOR THE IMPROVEMENT OF INTRAPERITONEAL DIAGNOSIS?

As described above, numerous efforts have been made to improve the detection of intraperitoneal free cancer cells. The purpose of most of these studies appeared to primarily be an improvement of the accuracy in cytology. The secondary purpose will be to make diagnosis more convenient and automatic than subjective conventional cytology. Once the accuracy and procedure is essentially improved over the conventional cytology, what should we do next? The identification of intraperitoneal free cancer cells confers poor prognosis. In patients with positive cytology without macroscopic peritoneal metastasis, the benefit of radical or aggressive surgery is still a matter of debate. While some of these patients are palliated, others may undergo more aggressive therapies. Along with the improved diagnostic modality, the treatment strategy would also have to be a coupled issue.

MULTIMODAL CLINICAL APPROACH FOR PERITONEAL SPREAD OF GASTRIC CANCER

Surgeons have witnessed some patients with peritoneal spread of gastric cancer who underwent radical surgery and experienced cures due to the recent improvements in multimodal treatment. A phase II study of whether gastrectomy with curative intent would be beneficial for patients with positive cytology but absence of macroscopic peritoneal seeding has been conducted[63,64]. The study showed that median overall survival time was 705 d, and the 5-year survival rate was 26% in the patients with positive cytology with no other non-curative factors, suggesting that surgery with curative intent could be indicated even for patients with positive cytology[63,64]. For gastric cancer patients with macroscopic peritoneal metastasis, Yamaguchi *et al*[65] evaluated intraperitoneal chemotherapy along with systemic chemotherapy as a phase II study. They reported a 1-year survival rate of 77.1%, which is surprisingly high. The same group also reported salvage gastrectomy after intravenous and intraperitoneal chemotherapy for the patients who had peritoneal metastasis but showed apparent shrinkage of their peritoneal nodules as well as negative cytology by the treatment[66]. Those patients who underwent salvage gastrectomy exhibited a 26.4-mo median survival period and 82% of 1-year overall survival. Those results suggested that the more sensitive and specific peritoneal diagnosis with the molecular approach might allow gastric cancer patients to receive more suitable individualized multimodal therapies.

A NEW MOLECULAR-TARGETING THERAPY FOR INTRAPERITONEAL SPREAD OF GASTRIC CANCER

Along with the research for the improvement in detection of intraperitoneal cancer cells, molecular targeting therapies might be derived from the results of basic research. One of the molecular targets is epithelial cell adhesion molecule (EpCAM), a type I transmembrane glycoprotein functioning as a homotypic intercellular adhesion molecule[67]. High-level EpCAM expression was observed in 90.7% of gastric cancer[68]. Catumaxomab is an artificially engineered, tri-functional bispecific monoclonal antibody; Fab binding sites bind to EpCAM on cancer cells and CD3 on T cells, and the Fc region binds and activates accessory immune cells. The tri-cell complex of T-cells, tumor cells and accessory cells induces MHC-unrestricted but specific efficient tumor cell killing. The therapeutic benefit of Catumaxomab for patients with malignant ascites including gastric cancer patients has been reported in a pivotal clinical trial[69], which led to approval of Catumaxomab by the European Medicines Agency (EMA) in 2009. Intraperitoneal Catumaxomab treatment has been shown to trigger the activation of immune effector cells in the peritoneal cavity resulting in the depletion of EpCAM-positive tumor cells[70]. Thus, local strategies with molecular targeting agents might represent the appropriate option for treatment of the peritoneal spread of gastric cancer.

CONCLUSION

In the past decade, enormous strides have been made in the research for molecular detection of intraperitoneal free gastric cancer cells, and many new strategies have been clinically tested in gastric cancer patients. As with the conventional cytology, none of the candidate alternatives to conventional cytology are a perfect modality yet, whereas most of them would potentially be conducive to improve the conventional diagnosis and to predict prognosis. The uncertainty of a definition of positivity in these novel approaches and their clinical relevance remain potential limitations to the practical clinical use of these technologies. Too highly sensitive techniques such as PCR may result in the detection of clinically irrelevant metastatic disease, which could lead to either overtreatment with unnecessary chemotherapy, or worse, the withdrawal of potentially curative surgical treatment. Nevertheless, the development of more sensitive and rapid diagnostics in evaluating minimal peritoneal disease is needed for patients to be properly treated. Since peritoneal lavage cytology has recently been included in the staging criteria of gastric cancer, the cytology diagnosis has been focused on as having an important predictive

role in gastric cancer treatment, and the molecular diagnosis has undergone tremendous challenges. With the accumulated evidence, the molecular diagnosis of peritoneal cytology may be a reality in future gastric cancer practice.

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ORIGINAL ARTICLE

Operative technique of antethoracic esophageal reconstruction with pedicled jejunal flap

Yasuhiro Shirakawa · Kazuhiro Noma · Takeshi Koujima · Naoaki Maeda · Shunsuke Tanabe · Toshiaki Ohara · Kazufumi Sakurama · Toshiyoshi Fujiwara

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Abstract
Background Esophageal reconstruction using intestine is often performed for esophageal cancer patients in cases where the stomach cannot be used. We have previously performed reconstruction using ileocolon with supercharge and drainage as our first choice in those cases. However, a less invasive, simpler, and safer reconstructive technique using jejunum without vascular anastomosis has recently become popular at our facility. This study describes the technique of esophageal reconstruction with jejunum, compares the surgical outcomes to those of standard reconstruction using ileocolon, and discusses the clinical significance of this new concept.
Patients and methods Subjects comprised 53 patients (52 males, 1 female) who underwent esophageal reconstruction using jejunum between January 2008 and July 2013. Patient characteristics, technical details, and outcomes were compared with those of 51 subjects who had undergone esophageal reconstruction using ileocolon. When making the pedicled jejunal flap, the first jejunal vascular arcade was preserved, which in most cases allowed it to be pulled up to the cervical region by processing and transection up to the second jejunal vascular branch.
Results The vascular anastomosis techniques were used in 80.4 % (41/51) of esophageal reconstructions using colon, compared with only 24.5 % (13/53) of reconstructions using jejunum. No difference in the frequency of postoperative adverse effects was seen between groups, but the frequency of diarrhea was significantly lower with reconstruction using jejunum.
Conclusion Esophageal reconstruction using jejunum with the blood vessel processing technique results in both simpler and safer pulling up. Thus the need to perform supercharge and superdrainage is reduced.

Keywords Esophageal reconstruction · Pedicled jejunal flap · Supercharge · Superdrainage

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Introduction

For the reconstruction after esophagectomy, the gastric tube is the first choice because it has a stable blood flow and only one point of anastomosis [1]. However, improved postoperative prognoses for gastric cancer and advances in diagnostic techniques have resulted in a greater number of esophageal cancer cases with the complication of asynchronous or synchronous gastric cancer. Many reports have described the usefulness of reconstruction using colon for such patients [1–11]. Reconstruction using the colon (particularly ileocolon) was previously the first choice in Japan and around the world when use of the stomach was impossible. We have also reported that supercharge and superdrainage techniques make ileocolic reconstruction safer [12]. However, in some cases performing ileocolic reconstruction necessitates detachment of the intestine from the retroperitoneum over a wide area, in order to pull the intestine up to the cervical region. Detachment of the mesentery can also be required. Furthermore, multiple gastrointestinal anastomoses are required at a minimum of 3 sites, carrying some degree of risk. In consideration of these issues, some patients have undergone two-stage

surgeries, because this technique is more invasive than reconstruction using a gastric tube. In addition to these technical issues, most patients suffer from postoperative diarrhea even beyond the acute perioperative state [4].

Another section of intestine that can be used for esophageal reconstruction is the jejunum, which offers several advantages because the diameters of the jejunum and esophagus are similar, fewer gastrointestinal anastomoses are required, and peristalsis can be maintained. However, compared with the colon, use of the jejunum has been considered to involve an unstable blood supply and difficulties in pulling up for feeding vessels [13]. The jejunum has therefore not been a common choice for reconstruction when the intestine must be pulled up to the cervical region. Longmire [14] reported the use of supercharge and superdrainage when pulling up the pedicled jejunal flap as effective for reducing troubles with the blood supply. In addition, advances in plastic surgical techniques have resulted in progressively more stable outcomes [15–18]. However, if the intestine could be safely pulled up without performing supercharge and superdrainage, the surgery would be less invasive, and operative time could be reduced. As we were cognizant of the anatomical features of the first jejunal vascular arcade, we devised a technique to pull up the pedicled jejunal flap safely by preserving this arcade and transection up to the second jejunal vascular branch (J2) in most cases. Using this technique, we could maintain the blood supply and drainage to the tip of the pulled-up intestine. Thus, since 2008, reconstruction using the jejunum has been used as the first-choice technique for cases in which esophageal reconstruction required the use of intestine. The present study, therefore, aimed to characterize and evaluate this technique by comparing its outcomes with those of the existing standard esophageal reconstruction technique using ileocolon with supercharge and superdrainage.

Materials and methods

Patients

We studied 53 patients (mean age 67.5; 52 males, 1 female) who underwent esophageal reconstruction using a pedicled jejunal flap at our facility between January 2008 and July 2013. These patients represent 15.3 % of the 346 patients who underwent surgery for esophageal cancer during the same period. Patient characteristics, technical details, and outcomes were compared with those of 51 subjects who had undergone esophageal reconstruction using the ileocolon between January 1998 and December 2004, as we previously reported (Table 1) [12]. During the period between 2005 and 2007, the policy of esophageal reconstruction method for the cases in which stomach could not be used was in transitional stage from ileocolic reconstruction to jejunal reconstruction. The processing methods for making jejunal flap described in this manuscript was not established. So we excluded the cases in this period.

Table 1 Clinical characteristics

	Jejunal reconstruction (2008–2013, $n = 53$)	Colonic reconstruction (1998–2004, $n = 51$)[a]	p
Age (years)	67.5 ± 7.3	64.2 ± 11.6	0.088
Sex			
Male	52	46	0.072
Female	1	5	
pTNM stage			
Stage 0	1	0	0.675
Stage I	6	4	
Stage II	8	11	
Stage III	32	31	
Stage IV	6	5	
Disease			
Postgastrectomy[b]	39	22	<0.001
Synchronous gastric cancer	14	6	
Bypass	0	3	
Others	0	20	
Operative procedure			
One-stage operation	34	8	<0.001
Two-stage operation	19	43	

[a] Referred to our previous report [12]

[b] Including 3 cases after total gastrectomy

Preoperative examination

For patients who have to undergo esophageal reconstruction using jejunum, in addition to the ordinary preoperative examination, we examine the anatomical branching pattern of superior mesenteric vessels on 3-dimensional computed tomography (CT) angiography (Fig. 1)

Operative procedure

Before pulling up the jejunal flap and preparing the jejunal vessels, it is critical to achieve and maintain complete awareness of the anatomical features of the blood flow to the first jejunal vascular arcade. After leaving the ligament of

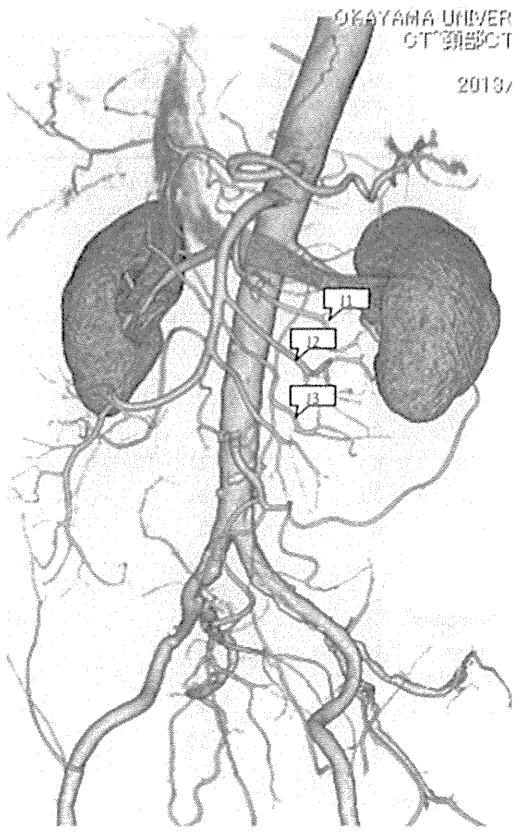

Fig. 1 3-dimensional CT angiography shows superior mesenteric artery and branch of it. *J1* the first jejunal vascular branch, *J2* the second jejunal vascular branch, *J3* the third jejunal vascular branch

Treitz, the first jejunal vascular branch (J1) often forms double or triple arcades before reaching the marginal vessels. Processing the vascular branches to preserve each arcade is critical (Fig. 2). The jejunum is transected ~3–5 cm from the ligament of Treitz. It is also important to preserve the vascular arcade around the proximal end of jejunum. In addition to the first blood vessels processing described above, J2 is normally transected, and the mesentery is cut out in a circular pattern to allow the jejunal flap to be pulled up to the cervical region (Figs. 2, 3a, b). However, in patients undergoing combined resection of the laryngopharynx or in patient who have only a short gap between J2 and the third jejunal vascular branch (J3), processing and transection must be performed up to J3 (Fig. 4a). If the patients underwent either Billroth II or Roux-en-Y reconstruction before, we should separate the joint of anastomosis first and redo the digestive tract reconstruction. For esophageal reconstruction with pedicled jejunal flap, the antethoracic route is usually chosen due to the possibility that supercharge and super-drainage will be required.

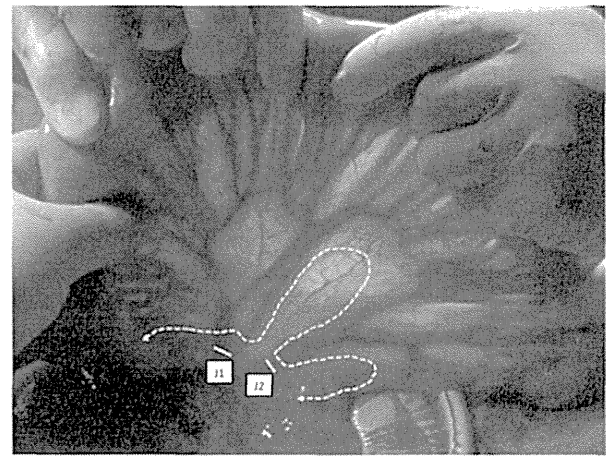

Fig. 2 Processing of jejunal vessels and the mesojejunum. Double or triple arcades of the first jejunal vascular branch are preserved, and the jejunum is transected as close as possible to the ligament of Treitz. The mesojejunum is cut out in a circular pattern. *J1* the first jejunal vascular branch, *J2* the second jejunal vascular branch

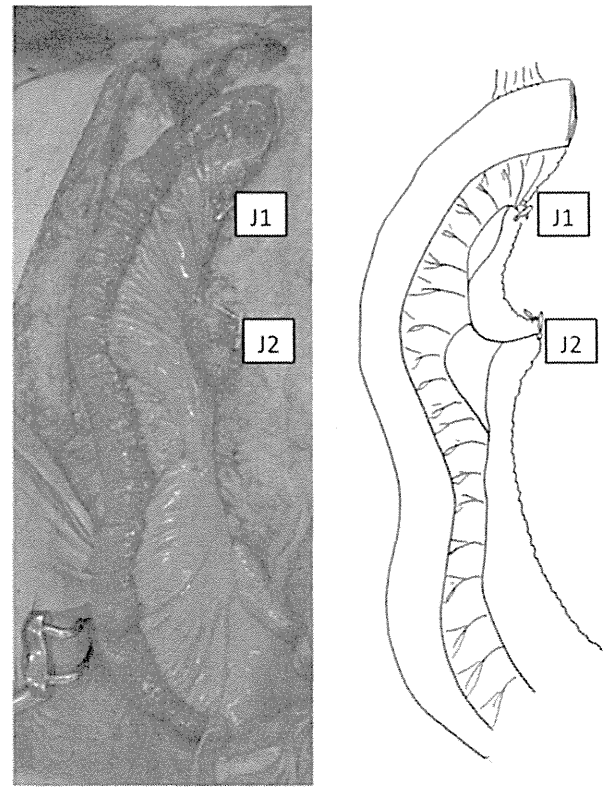

Fig. 3 Pulling up the pedicled jejunal flap using the antethoracic route. In 87.7 % (57/65) of cases, processing was performed up to the second jejunal vascular branch, and pulling up of the pedicled jejunal flap to the cervical region was possible. *J1* the first jejunal vascular branch, *J2* the second jejunal vascular branch

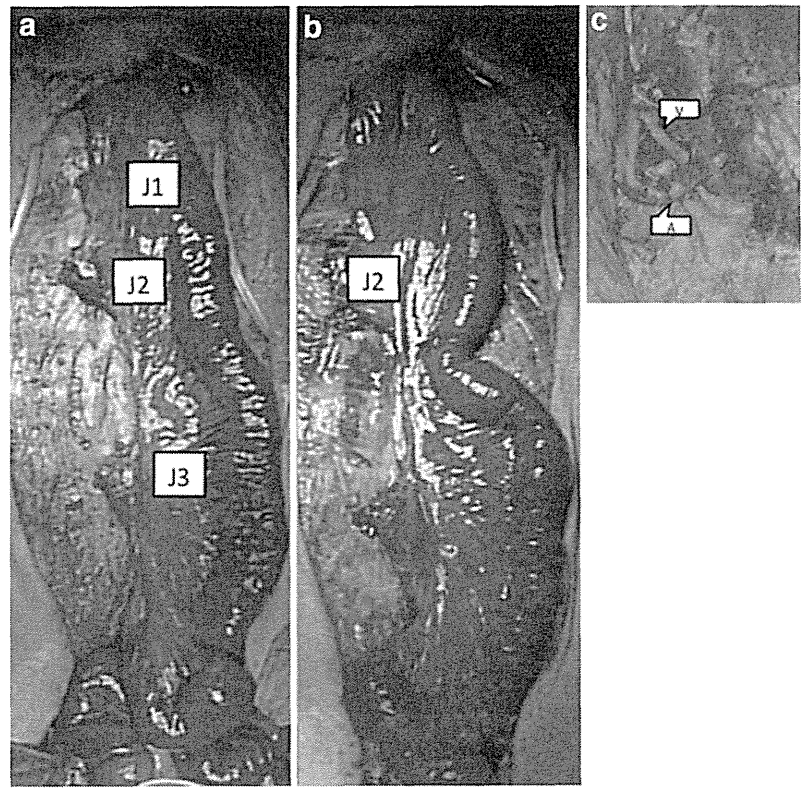

Fig. 4 **a** In 12.3 % (8/65) of cases, the pedicled jejunal flap needed to be processed up to the third jejunal vascular branch to further pull it up to the cervical region. **b, c** In most of these cases (5/8), both supercharge and superdrainage were necessary due to ischemia. *J1* the first jejunal vascular branch, *J2* the second jejunal vascular branch, *J3* the third jejunal vascular branch, *A* artery anastomosis, *V* vein anastomosis

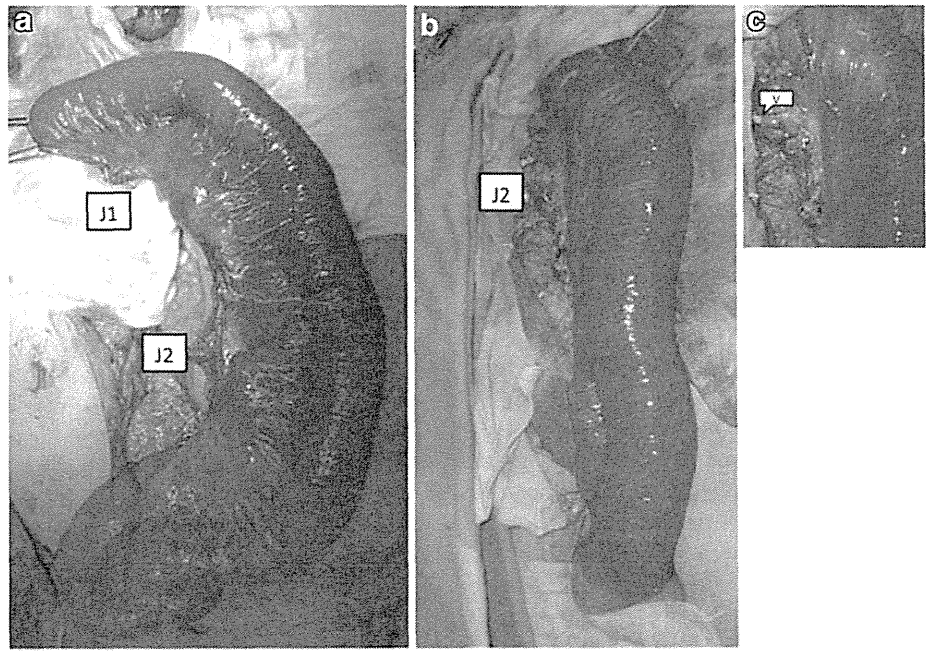

Fig. 5 **a** In 12.3 % (8/65) of cases, congestion in the pedicled jejunal flap happened. **b, c** In all of these cases, only superdrainage was necessary. *J1* the first jejunal vascular branch, *J2* the second jejunal vascular branch, *V* vein anastomosis

The criterion for performing supercharge or superdrainage is congestion for venous anastomosis and ischemia for arterial anastomosis. Congestion can be diagnosed relatively rapidly, whereas the diagnosis of ischemia takes longer (~30 min) and sometimes is difficult. When congestion is diagnosed, venous anastomosis is performed by a plastic surgery team prior to digestive tract anastomosis (Fig. 5a–c). However, when ischemia is suspected,

Table 2 Vessels for supercharge and superdrainage

	Jejunal reconstruction (2008–2013)	Colonic reconstruction (1998–2004)[a]
Recipient A		
Internal thoracic A	4/5	3/41
Transverse cervical A	1/5	37/41
Common carotid A	0/5	1/41
Recipient V		
Internal thoracic V	9/13	2/41
Transverse cervical V	1/13	0/41
Internal jugular V	0/13	5/41
External jugular V	0/13	33/41
Superficial cervical V	0/13	1/41
Brachial cephalic V	3/13	0/41

[a] Referred to our previous report [12]

esophago-jejunostomy is performed first; the blood supply is re-evaluated by checking the color and the peristalsis of intestine, and sometimes verifies the bleeding by cutting the small mesenteric artery. Arterial anastomosis can then be performed as necessary. In these cases, venous anastomosis is invariably also performed (Fig. 4b, c). When Roux-en-Y intestinal reconstruction is performed, the jejunal flap is pulled up, and the esophago-jejunostomy and jejuno-jejunostomy are both sutured manually in layer-to-layer method with 4-0 monofilament absorbable suture. Finally, an enteral feeding tube is inserted.

Description and statistical analysis

Clinicopathological factors were noted as per the 13th edition of the General Rules for Esophageal Cancer [19] and the Union for International Cancer Control Tumor Nodes Metastasis Classification of Malignant Tumors, 7th edition [20]. Postoperative complications were categorized as per the Clavien–Dindo classification [21]. Data are expressed as mean ± standard deviation. Statistical analysis was conducted using Student's *t* test, the Chi square test, or Fisher's exact test to suit the category in question. All analyses were performed using JMP version 11 statistical analysis software (SAS Institute, Cary, NC, USA).

Table 3 Complications

	Jejunal reconstruction (2008–2013, $n = 53$)	Colonic reconstruction (1998–2004, $n = 51$)[a]	p
Surgical complications			
Intestinal necrosis (Grade IIIa～)	0 (0.0 %)	0 (0.0 %)	1.000
Bleeding (Grade IIIa～)	0 (0.0 %)	1 (2.0 %)	0.234
Anastomotic leakage (Grade IIIa～)	4 (7.5 %)	4 (7.8 %)	0.932
Anastomotic stenosis (Grade IIIa～)	4 (7.5 %)	7 (13.7 %)	0.303
Ileus (Grade II～)	1 (1.9 %)	2 (3.9 %)	0.532
Medical complications			
Heartburn (Grade II～)	0 (0.0 %)	0 (0.0 %)	1.000
Dumping syndrome (Grade II～)	2 (3.8 %)	0 (0.0 %)	0.098
Diarrhea (Grade II～)	0 (0.0 %)	20 (39.2 %)	<0.001

Complications are described on the Clavien–Dindo classification [16]

[a] Referred to our previous report [12]

Results

Thirty-nine patients had a past history of gastrostomy, 14 had synchronous stomach cancer. Gastrectomy patients included 3 with a past history of total gastrectomy (Table 1). Eight patients (15.1 %) required processing and transection up to the third jejunal vascular branch. Of the 13 patients (24.5 %) who required vascular anastomosis, 8 (15.1 %) required only superdrainage due to congestion, and 5 (9.4 %) required both supercharge and superdrainage due to ischemia (Table 2). Among the latter group, all 5 patients underwent processing and transection up to J3. In most cases, intrathoracic arteries and veins were utilized as recipient vessels, but the brachial cephalic vein has recently been used more frequently. A two-stage operation was selected to reduce surgical invasiveness for 19 (35.8 %) of those cases that underwent reconstruction using jejunum. This represented a significant decrease in frequency compared to the 43 cases (84.3 %; $p < 0.0001$) with reconstruction using ileocolon (Table 1).

Table 4 Relationships between the status (with/without) vascular anastomosis and postoperative complications

	Without vascular anastomosis (2008–2013, $n = 40$)	With vascular anastomosis (2008–2013, $n = 13$)	p
Surgical complications			
Intestinal necrosis (Grade IIIa∼)	0 (0.0 %)	0 (0.0 %)	1.000
Bleeding (Grade IIIa∼)	0 (0.0 %)	0 (0.0 %)	1.000
Anastomotic leakage (Grade IIIa∼)	3 (7.5 %)	1 (7.7 %)	0.982
Anastomotic stenosis (Grade IIIa∼)	2 (5.0 %)	1 (7.7 %)	0.724
Ileus (Grade II∼)	1 (1.8 %)	0 (3.9 %)	0.451
Medical complications			
Heartburn (Grade II∼)	0 (0.0 %)	0 (0.0 %)	1.000
Dumping syndrome (Grade II∼)	2 (5.0 %)	0 (0.0 %)	0.289
Diarrhea (Grade II∼)	0 (0.0 %)	0(0.0 %)	1.000

Complications are described on the Clavien–Dindo classification [16]

Surgical complications did not include necrosis of the pulled-up intestine, but 7.5 % of patients experienced anastomotic leakage, and 1.9 % of patients suffered from ileus. There were no instances of complications, such as hemorrhage, caused by supercharge or superdrainage in cases in which these procedures were performed. No significant differences were seen in the frequency of any specific surgical complication or in the overall frequency of surgical complications between cases of jejunal and colonic reconstruction. No cases of diarrhea (Grade II or more in the Clavien–Dindo classification) were encountered after jejunal reconstruction, and a significant difference was seen between the jejunal and colon reconstruction groups in the frequency of diarrhea ($p < 0.0001$, Table 3). On the other hand, there were no significant differences in surgical or medical complication rate between the cases with vascular anastomosis and those without vascular anastomosis (Table 4). The abdominal and reconstructive operative time were significantly shorter ($p = 0.0037$) in the cases without vascular anastomosis ($n = 40$; 340 ± 53 min) than in the cases with vascular anastomosis ($n = 13$; 642 ± 141 min).

Discussion

When esophageal reconstruction is performed using jejunum after total pharyngo-laryngo-esophagectomy or cervical esophagectomy for the cancer of hypopharynx or cervical esophagus, respectively, a free flap is often used for reconstruction [22–25]. Our previous study confirmed the effectiveness of this technique [26]. However, when performing reconstruction using a pedicled intestinal flap, most studies have shown advantages of colonic flap [1–11]. Particularly when using ileocolon, careful dislodgement from the retroperitoneum allows stable pulling up. However, some problems are seen in that procedure, including the numerous variations of ileocolic and cecal blood vessels, which mean that blood flow can be difficult to confirm after making the flap. We have previously reported that supercharge and superdrainage have led to satisfactory outcomes in most cases of ileocolonic reconstruction [12]. Another problem is that some cases require wide detachment from retroperitoneum up to the mesentery, making the surgery more invasive. Other cases show problems of bending of the elevated intestine and postoperative diarrhea [4], which are closely related to postoperative quality of life (QOL).

On the other hand, pedicled jejunal reconstruction has normally been used after total gastrectomy and fundectomy [27]. When making a jejunal flap, blood vessel processing is relatively easy, and detachment from the retroperitoneum is not necessary in almost all cases. Anastomosis is comparatively easy because the diameters of jejunum and esophagus are similar, and less anastomoses are required as well. However, jejunum is generally more difficult to pull up than colon, and pulling up to the cervical region is particularly difficult due to the formation of jejunal vascular branches and the blood circulation. High pulling up with processing and transection of only one jejunal vascular branch is normally difficult, so pulling up the jejunal flap safely to a high elevation can be performed by processing and transection of at least two or three jejunal vascular branches (generally the second to fourth jejunal vascular branches are selected) and performing supercharge and superdrainage [15–18]. Furthermore, a technique has been described involving transection of the vascular arcades bordering the jejunal vascular branches to elongate the mesentery and then performing supercharge and superdrainage [18, 28].

In our technique, we process and transect J1 and J2 with preservation of the arcade of J1. Utilizing this technique, pulling up the jejunal flap to the cervical portion is possible in most cases, and supercharge and superdrainage are not necessary in ~75 % of cases. This may be attributable to two reasons. First, preserving the arcade of the first branch may lead to good blood circulation (especially in venous return) around the tip of the intestine. We suggest that most cases of trouble with blood circulation are caused by inadequate venous return followed by weakened arterial perfusion. In other words, improvement of drainage would have improved our outcomes. Second, our method of processing jejunal vessels is advantageous to elongate the mesentery.

Although supercharge and superdrainage were still necessary in ~25 % of cases, congestion can be diagnosed relatively quickly, so determining whether superdrainage is necessary is easy. Nevertheless, most cases of ischemia require additional time to diagnose, so it is necessary to proceed with caution. Temperature of the intestine and the status of peristalsis are occasionally important indicators of ischemia. It is also important to consult with the plastic surgery team that will perform the vascular anastomosis, so that the gastrointestinal and plastic surgical teams can perform the evaluation together. In this study, however, only 5 cases required both supercharge and superdrainage, and in each of those cases, processing and transection were performed up to J2 and J3. Thus, in cases in which this blood vessel processing is required, supercharge and superdrainage will probably also have to be performed. We determine the appropriateness of vascular anastomosis based on these criteria, and have never observed jejunal flap necrosis in any cases with or without vascular anastomosis. We therefore consider our criteria to be adequate. When vascular anastomosis is performed, cervical blood vessels are often selected in reconstruction cases utilizing the colon [12]. However, in reconstruction cases utilizing the jejunum, J2 is almost always selected as a donor vessel, and intrathoracic arteries and veins are often selected as recipient vessels due to their anatomical positions if necessary. For these reasons, we choose the antethoracic route in all cases when pulling jejunal flap to cervical region. While this route does carry cosmetic disadvantages, we choose this route in which the recipient vessels can be obtained easily because vascular anastomosis is necessary at least in 25 % cases of jejunal flap construction performed at our facility. Another reason for choosing the antethoracic wall route is the difficulty in evaluating the blood supply when utilizing another route.

On the other hand, we have reported a technique in which the stomach is preserved and the pedicled jejunum is pulled up via the posterior mediastinal route for cases in which cancer lesions are limited to the lower thorax or abdominal esophagus and do not reach the stomach [29]. When a long section of esophagus remains preserved, performing anastomosis between the esophagus and stomach directly within the mediastinum frequently leads to the reflux of gastric acid or bile, markedly reducing QOL for patients. However, our study showed that utilizing this technique leads to less reflux and a lower incidence of dumping syndrome [29]. For cases in this study in which the stomach was resected and reconstruction was performed via the antethoracic wall route, the frequencies of reflux or dumping syndrome were also low. In addition, diarrhea, as a relatively common problem in reconstructions utilizing the colon [4], was not observed in reconstructions utilizing the jejunum. Other studies have indicated that reconstructions utilizing the jejunum are less frequently accompanied by weight loss [30], representing an advantage from the perspective of QOL. Furthermore, in this study, we experienced 3 cases of jejunal flap reconstruction in patients who had previously undergone total gastrectomy. Because it was even possible to utilize jejunum that had been used in previous reconstructive surgeries without difficulty, the use of ileocolon for this procedure will likely decrease at our facility.

In conclusion, supercharge and superdrainage are not usually required when esophageal reconstruction is performed with jejunum according to our concept of blood vessel processing. This technique reduces operative time and is less invasive. In addition, when this technique is utilized, postoperative diarrhea is infrequent. In cases of esophageal cancer in which stomach cannot be used, the reconstruction utilizing jejunum could represent the technique of choice.

Ethical Statement Our present study is performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights, and we followed the policy concerning informed consent as shown on http://Springer.com. Informed consent was obtained from all the study participants.

Present study is a retrospective study, but it should be performed in accordance with the ethical standards laid down in the Declaration of Helsinki and all subsequent revisions.

We protect the confidentiality of the privacy of the patients on the presentation of research results. And we do not use any information obtained from present studies for other purpose.

Conflict of interest There are no financial relations that could lead to a conflict of interest.

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症例報告

術前 DCF 療法が著効した食道原発内分泌細胞癌の 1 切除例

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Complete response of primary esophageal endocrine cell carcinoma resected after neoadjuvant chemotherapy with docetaxel/cisplatin/5-fluorouracil

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Esophageal endocrine cell carcinoma is extremely rare. We report a case of esophageal endocrine cell carcinoma showing histological complete response to neoadjuvant chemotherapy with docetaxel/cisplatin/5-fluorouracil (DCF). A 66-year-old man had been experiencing epigastralgia, and a type 2 tumor in the thoracic part of esophagus was detected by upper endoscopy. The biopsy showed endocrine cell carcinoma. PET/CT, endoscopy and an esophagogram showed that the patient had a 70-mm scaled type 2 tumor in the middle thoracic esophagus, and they also revealed lymph node metastases (no. 106recR). We diagnosed a cT3cN1cM0 cStage III tumor. With two courses of DCF treatment, both the primary tumor and lymph node metastases showed a partial response. We performed a subtotal esophagectomy with three-field lymph node dissection. The pathological examination of the resected specimens revealed no malignant cells in the esophagus or lymph nodes, and we concluded that the pathological effect of the DCF treatment was Grade 3.

キーワード：食道癌 (esophageal cancer), 内分泌細胞癌 (endocrine cell carcinoma), DCF 療法 (DCF treatment)

はじめに

日本食道学会の Comprehensive Registry of Esophageal Cancer in Japan, 2003によれば食道内分泌細胞癌（小細胞型）は食道癌の0.6%とされる非常にまれな疾患であり，その予後は不良とされている[1-3]．本疾患の治療は，手術のみならず化学療法を含めた集学的な治療が必要とされている[4,5]．今回，docetaxel, cisplatin, 5-fluorouracil 三剤併用の術前化学療法（DCF 療法）が著効した胸部食道内分泌細胞癌（小細胞型）の 1 切除例を経験したので報告する．

症　例

患　者：66歳，男性
主　訴：心窩部痛
生活歴：喫煙 20本×40年，飲酒 ビール350ml/日．
既往歴：高血圧（内服加療中）．

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現病歴：心窩部痛のためかかりつけ医を受診し，上部消化管内視鏡検査を受け，胸部食道に半周性の 2 型病変を指摘された．生検で低分化扁平上皮癌または小細胞癌と診断され，精査加療目的に当科に紹介となった．
初診時現症：身長165.0cm，体重71.2kg．頸部から鎖骨上窩リンパ節は触知せず．
初診時検査所見：貧血は認めず，肝腎機能等の生化学検査異常も認めなかった．腫瘍マーカーは SCC 1.3ng/ml, CEA 1.77ng/ml, NSE 12.48ng/ml, ProGRP 34.9pg/mlといずれも正常値であった．
上部消化管造影検査（UGI）所見：胸部中部食道（Mt）左一前壁に，70mm大の周堤隆起明瞭な 2 型病変を認めた（図 1 A）．
上部消化管内視鏡検査（EGD）所見：切歯より25cm～33cmの食道左一前壁に半周性の 2 型病変を認めた（図 2 A）．口側には 1 型様の隆起部分もあり，特殊型を疑う形状であったため，同部位の生検を施行した．生検組織は HE 染色にてクロマチン濃度の上昇した N/C 比の高い異型細胞の増殖を認め，また免疫染色では synaptophysin 陽性であった（図 3）．以上より，内分泌細胞癌（小細胞型）と診断された．