

# Gastric tube cancer after radical esophagectomy: comparison of two periods in a single center

Eisuke Booka<sup>1</sup> · Hiroya Takeuchi<sup>1</sup> · Nobuhiko Okamoto<sup>1</sup> · Yusuke Uchi<sup>1</sup> · Kazumasa Fukuda<sup>1</sup> · Rieko Nakamura<sup>1</sup> · Tsunehiro Takahashi<sup>1</sup> · Norihito Wada<sup>1</sup> · Hirofumi Kawakubo<sup>1</sup> · Soji Ozawa<sup>2</sup> · Tai Omori<sup>1</sup> · Yuko Kitagawa<sup>1</sup>

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## Abstract

**Background** Recent improvements in the survival of patients after esophagectomy have led to an increasing occurrence of gastric cancer in the reconstructed gastric tube (GTC). The aim of this study was to assess generational changes in the clinicopathological characteristics and treatment of GTCs in a single center.

**Methods** Thirteen GTC lesions in ten patients were diagnosed and treated at Keio University Hospital between 2006 and 2014. In our previous study, we reported eight cases of GTC [1]. We compared clinicopathological characteristics and treatment of GTC, as well as overall survival achieved in this study with those in our previous study [1].

**Results** In this study, median patient age at the time of GTC detection was 74 years (range 62–81 years) and the median interval between esophagectomy and GTC detection was 95 months (range 21–159 months). Nine (69 %) of 13 lesions satisfied the criteria for endoscopic resection. On comparing this study with our previous study, there were no significant differences in patient age at the time of GTC detection, the interval between esophagectomy and GTC detection, or pathological stage [1]. Compared with our previous study, the use of less invasive treatments, such as endoscopic submucosal dissection and partial gastric tube resection with sentinel lymph node dissection, generationally increased and a significant difference was observed in

the type of GTC treatment [1]. However, there was no significant difference in overall survival between the studies.

**Conclusion** Long-term periodic endoscopy permits less invasive treatments and combinations of various treatments for effective GTC therapy.

**Keywords** Esophageal cancer · Gastric cancer · Gastric tube cancer · Endoscopic resection · Endoscopic submucosal dissection

## Introduction

Recent improvements in patient survival after esophagectomy have led to an increasing occurrence of gastric cancer in the reconstructed gastric tube (GTC) [2–5]. Synchronous gastric cancer reportedly accounts for 30 % of all multiple cancers, while metachronous head and neck cancers account for 21 % and cancer in the reconstructed gastric tube accounts for 7 % [1]. Thus, successful therapy of such lesions is very important, particularly in patients with good prognosis after esophagectomy.

Although patients with primary esophageal cancer undergo annual follow-up endoscopic examinations after esophagectomy, GTC may be difficult to diagnose because of suboptimal visualization caused by residual food that is frequently observed after esophagectomy with gastric tube reconstruction [6]. Surgical removal of the reconstructed gastric tube has been reported to be a more invasive procedure with high risk of postoperative morbidity and mortality [7]. Nowadays, the use of endoscopic resection as an alternative to surgical resection has increased [6, 8]. Although >200 cases of GTC have been reported in the literature to date, most of these were case reports that described only surgical and pathological results based on

✉ Hiroya Takeuchi  
htakeuchi@a6.keio.jp

<sup>1</sup> Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

<sup>2</sup> Department of Gastroenterological Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan

**Table 1** Esophageal cancer profiles of 10 patients

Case	Age	Sex	Location	Histology	pStage (UICC 6 th)	Approach	Reconstructed route
1	68	M	Lt	SCC (G2)	I	Thoracotomy	Posterior-mediastinal
2	58	M	Lt	SCC (G2)	III	Thoracotomy	Antesternal
3	68	M	Mt	SCC (G2)	I	Thoracotomy	Antesternal
4	68	M	Lt	Ad (G3)	III	Thoracoscopic	Posterior-mediastinal
5	59	M	Mt	SCC (G2)	I	Thoracoscopic	Posterior-mediastinal
6	58	M	Mt	SCC (G1)	I	Thoracotomy	Posterior-mediastinal
7	63	M	Mt	SCC (G2)	I	Thoracoscopic	Posterior-mediastinal
8	57	F	Mt	SCC (G3)	IIA	Thoracoscopic	Posterior-mediastinal
9	67	M	Lt	SCC (G1)	IIA	Thoracotomy	Intrathoracic
10	63	M	Ut	SCC (G2)	IIB	Thoracoscopic	Posterior-mediastinal

*Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *SCC* squamous cell carcinoma, *Ad* adenocarcinoma, *G1* well-differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *UICC* International Union Against Cancer

short-term observations [9]. To date, no report in the literature has described generational changes in the clinicopathological characteristics and treatment of GTC in a single center.

In our previous study, we reported eight cases of GTC after esophagectomy, two (25 %) of which satisfied the criteria for endoscopic resection and five (63 %) histopathologically underwent curative resection, two by endoscopy, and three by surgery [1]. In that study, we concluded that early diagnosis allowed for less invasive treatment of metachronous gastric carcinoma arising from the reconstructed gastric tube, and strict postoperative examinations were important after radical esophagectomy to ensure early detection, although curative treatment is difficult in advanced cases [1]. We hypothesized that improvements in endoscopic techniques and expansion of criteria of endoscopic resection contributed to the early detection of GTC and an opportunity for less invasive treatment. We compared clinicopathological characteristics and treatment of GTC, as well as overall survival achieved in the present study with those in our previous report [1].

## Patients and methods

### Patients

We defined GTC as a newly developed cancer in the gastric tube that was used as an esophageal substitute after esophagectomy. Metachronous multiple primary carcinoma was defined according to the following criteria as described by Warren and Gates: (1) clearly malignant tumors on histologic examination, (2) separated by normal mucosa, and (3) exclusion of a possible second metastatic tumor [1]. A total of 13 GTC lesions in ten patients that satisfied these criteria were diagnosed and treated at Keio University

Hospital between 2006 and 2014. The esophageal cancer profile of ten patients is shown in Table 1. All patients underwent esophagectomy for esophageal cancer at our hospital between 1993 and 2010. Most (90 %) patients were male (median age 63 years; age range 57–68 years) with squamous cell carcinoma at the time of esophagectomy. The procedure consisted of total or subtotal thoracic esophagectomy through a right thoracotomy in five (50 %) patients or thoracoscopy in five (50 %) patients with regional lymph node dissection. The route of gastric tube reconstruction was posterior mediastinal in seven (70 %) cases, antesternal in two (20 %) cases, and intrathoracic in one (10 %) case. Case 4 received adjuvant chemotherapy because of highly advanced esophageal cancer.

Each patient underwent periodic physical and laboratory examinations at 2- or 3-month intervals. Computed tomography was performed every 6 months and periodic endoscopy was annually performed.

### Methods

Clinicopathological characteristics, including symptoms, diagnostic tools, intervals between esophagectomy and detection of GTC, and treatment modalities, were retrospectively analyzed. Metachronous GTC (Cases 3 and 9) and double GTCs (Case 10) were individually investigated. Esophageal tumor location was described according to the International Union Against Cancer (UICC) 6th edition tumor–node–metastasis (TNM) classification system [10]. To describe the GTC location, we divided the gastric tube into three regions: upper, middle, and lower third. The histopathological type of carcinoma of the esophagus and gastric tube was determined according to the Japanese Classification of Esophageal Cancer and Gastric Carcinoma, respectively [11, 12]. Histopathological grading, depth of

tumor invasion, regional nodal status, distant metastatic disease, and clinical and pathological staging of esophageal cancer and GTC were classified according to the UICC 6th edition TNM classification for cancer of the esophagus and stomach, respectively [10]. For GTC cases treated by endoscopic resection, indications for endoscopic resection and histopathological criteria for curative or non-curative endoscopic resection were based on the Japanese Gastric Cancer Association Gastric Cancer Treatment Guidelines 2010 (ver. 3) [13]. We compared clinicopathological characteristics, treatment of GTC, and overall survival of this study with those of our previous study [1].

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA). Categorical data were analyzed using Fisher's exact test or  $\chi^2$  test when appropriate. A probability ( $p$ ) value of  $<0.05$  was considered statistically significant. Survival outcomes were analyzed using the Kaplan–Meier method and log-rank tests.

## Results

### Patient and clinicopathological characteristics

The esophageal cancer profiles of ten patients are summarized in Table 1 and GTC profiles of 13 lesions are summarized in Table 2. The median age at the time of GTC detection was 74 years (range 62–81 years) and the median interval between esophagectomy and GTC detection was

95 months (range 21–159 months). A total of 8 (62 %) lesions developed in the lower third of the gastric tube. All lesions were detected by periodic endoscopy and all patients were asymptomatic. Histopathological examination of the biopsy specimens revealed that all GTCs were diagnosed as adenocarcinoma and two (15 %) were well-differentiated adenocarcinoma (G1), five (38 %) were moderately differentiated adenocarcinoma (G2), and six (46 %) were poorly differentiated adenocarcinoma (G3). The tumors invaded the muscularis propria in Cases 2 and 6. The depths of the other 11 tumors (85 %) were T1 and the GTCs were considered to be early gastric cancers. There was no evidence of distant metastasis in any patient.

### Treatment

Of all lesions, nine (69 %) fulfilled the indications for endoscopic resection and were resected en bloc by endoscopic submucosal dissection (ESD) without serious adverse events [13]. The results of pathological examinations of the specimens resected via ESD showed that complete resection was performed in all nine cases. Furthermore, resection of six (67 %) lesions was judged to be curative according to the Japanese Gastric Cancer Association criteria [13]. No disease recurrence was observed in any of the six cases judged to be curative resection during a median follow-up period of 18 months (range 4–50 months). Of the three (33 %) non-curative cases, additional treatment with S-1 (Taiho Pharmaceutical, Tokyo, Japan) and proton therapy was performed for Case 7. This patient did not develop recurrence. In Cases 3–2, the horizontal and vertical margins of the resected specimen were unclear. However, this

**Table 2** Gastric tube cancer profiles of 13 lesions in 10 patients

Case	Age	Interval (months)	Location	Histology/depth	Treatment	Cur	Additional treatment	Prognosis (months)
1	81	153	Lower	G2/sm	APC	A		37, alive
2	61	33	Lower	G3/mp	CRT + partial resection	A		91, alive
3–1	81	154	Lower	G2/m	ESD	A		50, alive
3–2	81	159	Middle	G2/m	ESD	B	Strict follow-up	46, alive
4	72	45	Lower	G3/sm	ESD (palliative)	C	none	20, dead
5	72	157	Lower	G3/m	ESD	A		41, alive
6	62	42	Middle	G2/mp	Partial resection + SLND	A		33, alive
7	65	21	Middle	G3/sm	ESD	C	S-1 + proton therapy	26, alive
8	63	79	Lower	G3/m	ESD	A		21, alive
9–1	74	77	Middle	G3/m	ESD	C	Re-ESD	22, alive
9–2	75	95	Middle	G2/sm	ESD	A		4, alive
10–1	75	148	Lower	G1/m	ESD	A		18, alive
10–2	75	148	Lower	G1/m	ESD	A		18, alive

G1 well-differentiated, G2 moderately differentiated, G3 poorly differentiated, m mucosa, sm submucosa, mp muscularis propria, APC argon plasma coagulation, CRT chemoradiotherapy, ESD endoscopic submucosal dissection, SLND sentinel lymph node dissection, Cur A absolutely no cancer residual, Cur B neither Cur A nor Cur C, Cur C cancer residual, S-1 Taiho Pharmaceutical, Tokyo, Japan

**Table 3** Comparison of the clinicopathological characteristics between 13 lesions in this study and 8 lesions in our previous study [1]

	This study	Our previous study	<i>p</i> value
<b>Esophageal cancer</b>			
Age (years)			0.413
Median	63	63.5	
Range	57–68	57–72	
Gender			0.867
Male	9	7	
Female	1	1	
Histopathological type			0.357
Squamous cell carcinoma	9	8	
Adenocarcinoma	1	0	
Histopathological grading (UICC 6th)			0.914
G1	2	2	
G2	6	4	
G3	2	2	
pStage (UICC 6th)			0.353
I	5	4	
IIA	2	0	
IIB	1	3	
III	2	1	
Approach			0.019
Thoracoscopic	5	0	
Thoracotomy	5	8	
Reconstructed route			0.008
Antesternal	2	0	
Posterior-mediastinal	7	1	
Intrathoracic	1	2	
Retrosternal	0	5	
<b>Gastric tube cancer</b>			
Interval (months)			0.777
Median	95	91.5	
Range	21–159	30–221	
Diagnostic tool			0.166
Periodic endoscopy	13	6	
Upper GI	0	1	
Serum CEA	0	1	
Symptom			1.000
Symptomatic	0	0	
Asymptomatic	13	8	
Location			0.388
Upper third of the gastric tube	0	1	
Middle third of the gastric tube	5	2	
Lower third of the gastric tube	8	5	
Histopathological type			1.000
Adenocarcinoma	13	8	
Others	0	0	
Histopathological grading (UICC 6th)			0.503
G1	2	3	

**Table 3** continued

	This study	Our previous study	<i>p</i> value
G2	5	2	
G3	6	3	
Treatment			0.003
ESD	10	0	
EMR	0	3	
APC	1	0	
Surgery	1	3	
CRT → surgery	1	0	
BSC	0	2	

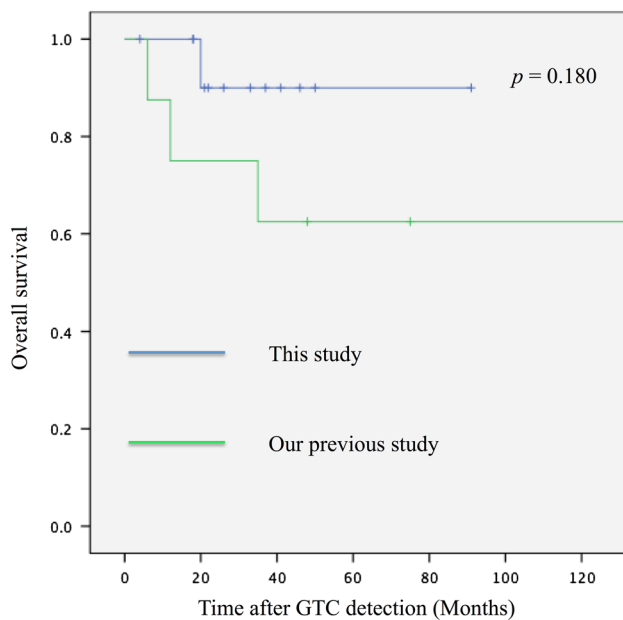
*G1* well-differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *UICC* International Union Against Cancer, *Upper GI* upper gastrointestinal series, *CEA* carcinoembryonic antigen, *ESD* endoscopic submucosal dissection, *EMR* endoscopic mucosal resection, *APC* argon plasma coagulation, *CRT* chemoradiotherapy, *BSC* best supportive care

patient did not receive additional treatment and experienced no recurrence of disease. In Cases 9–1, the horizontal margin was positive and the patient was followed up without any additional treatment; however, the patient developed recurrence 18 months after endoscopic resection. For local recurrence in this patient, ESD was performed again, which resulted in expanded curative resection [13].

The other 4 (31 %) lesions did not fulfill the indications for endoscopic resection [13]. Case 1 received argon plasma coagulation (APC) therapy and did not develop recurrence. Salvage gastric tube partial resection after concurrent chemoradiotherapy was performed in Case 2 and the patient did not develop disease recurrence. In Case 6, partial gastric tube resection with sentinel lymph node dissection was performed and the patient did not develop recurrence. In Case 4, palliative ESD was performed as a relative indication in consideration of the patient's physical condition and resulted in non-curative resection. The patient received no additional therapy because of poor general condition and died from peritoneal dissemination. In this case, it was difficult to distinguish between esophageal cancer recurrence and GTC recurrence 20 months after ESD and 45 months after esophagectomy.

### Comparison of our present and previous studies

Comparisons of the clinicopathological characteristics between 13 lesions in this study and eight in our previous study [1] are shown in Table 3. There were no significant differences in patient age at the time of GTC detection, the interval between esophagectomy and GTC detection, or pathological stage [1]. Compared with our previous study, the use of less invasive treatments, such as ESD and partial



**Fig. 1** Overall survival rate in our present and former [1] studies after GTC treatment

gastric tube resection with sentinel lymph node dissection, generationally increased and a significant difference was observed in the type of GTC treatment [1]. However, there was no significant difference in overall survival between the studies (Fig. 1).

## Discussion

As recent advances in diagnostic and treatment modalities for esophageal cancer improve patient survival after esophagectomy, the occurrence of GTC continues to increase [7, 14]. Thirteen GTC lesions were detected over a 9-year period in this study, while eight GTC lesions were detected among patients who underwent esophagectomy at our hospital over an 18-year period, as described in our previous study [1]. The lack of significant differences in patient age at the time of GTC detection and the interval between esophagectomy and GTC detection suggests that the incidence of GTC will increase as prognosis after esophagectomy improves [1]. GTC has emerged as a new clinical problem that must be solved to maintain patient quality of life after esophagectomy [9].

Most of the GTC lesions in this study and our previous study were located in the middle or lower third of the gastric tube, which suggests that bile reflux plays an important role in the development of GTC [1, 14, 15]. Significant differences were observed in the route of reconstruction applied in our hospital, as the preferable route is presently posterior mediastinal, while the retrosternal route

was formerly preferred. However, it remains unclear as to whether the route of reconstruction plays an important role in the development of bile reflux and emergence of GTC [16, 17]. There had been no clear evidence on the proportion of *H. pylori* infection in GTC patients in previous studies [1, 14]; however, more recently, it was reported that 98 % of GTC patients were positive for *H. pylori* gastritis, based on the histopathological assessments [6]. *H. pylori* infection is considered to play an important role in the development of GTC as well as bile reflux, and *H. pylori* eradication therapy may be considered to prevent the development of GTC after esophagectomy [6].

In our previous study, we emphasized the importance of early diagnosis, which allows for less invasive treatment of GTC [1]. After our previous study, we continued to perform annual endoscopy even >10 years after esophagectomy. By performing periodic endoscopy, we were able to detect all instances of GTC and identified six (46 %) of 13 lesions 10 years after esophagectomy. However, two (15 %) of these 13 lesions were detected at an advanced stage of gastric cancer. GTC may be difficult to diagnose because of suboptimal visualization caused by residual food [6]; therefore, more frequent periodic endoscopy, such as a 6-month interval, could be recommended. However, both these lesions were cured by salvage gastric tube partial resection after concurrent chemoradiotherapy or partial gastric tube resection with sentinel lymph node dissection. No recurrence was detected in these two cases during the follow-up periods of 91 and 33 months, respectively.

Total and distal gastrectomies for GTC are highly invasive and problematic to perform in patients who previously underwent radical esophagectomy [7]. Comparisons between our former and present studies revealed significant differences in the choice of treatments for GTC. For example, we now perform less invasive treatments, such as ESD, as the first choice for early GTC. Our finding of no significant difference between overall survivals suggests that patients benefited from less invasive therapy [1]. To performing a less invasive procedure, strict long-term follow-up is mandatory after esophagectomy.

Endoscopic resection is widely used for the treatment of early primary gastric carcinoma and this technique is potentially applicable to GTC [18, 19]. Moreover, the recent introduction of ESD has facilitated an increase in the rate of curative resection [6, 8]. However, it was reported that the proportions of en bloc, en bloc with tumor-free margins, and curative resections were lower than regular gastric ESD results [6]. These lower proportions could be caused by factors such as difficulty in visualization of lesion margins because of the long and narrow anastomotic structure of the reconstructed gastric tube [6]. Because ESD for GTC is more difficult than regular gastric ESD, performing a careful ESD procedure is required for GTC.



In this study, no cancer recurrence developed after curative ESD during a median follow-up period of 18 months (range 4–50 months), suggesting that ESD is a feasible and effective treatment method for GTC. For the treatment of local recurrence after non-curative ESD, re-ESD achieved successful results for Cases 9–1. This result suggests that strict follow-up is a possible alternative to additional surgery after non-curative ESD. Moreover, no cancer recurrence developed with the addition of S-1 + proton therapy after non-curative ESD in Case 7. However, in this study, there was no evidence that S-1 + proton therapy suppressed recurrence of non-curative lesions.

With regard to treatment of GTC beyond endoscopic indications, no cancer recurrence developed after APC therapy, salvage partial gastric tube resection after concurrent chemoradiotherapy, or partial gastric tube resection with sentinel lymph node dissection [20–24]. Although there was no evidence that these therapies are appropriate for advanced GTC, these therapies were found to be effective for advanced GTC in our study and, particularly, partial gastric tube resection with sentinel lymph node dissection contributed the preservation of the right gastroepiploic artery, which was the only feeding artery of the reconstructed gastric tube after esophagectomy. It is possible that partial gastric tube resection with sentinel lymph node dissection will become a new treatment choice for GTC [20–27]. A combination of sentinel lymph node dissection and ESD for GTC is another attractive option as a novel, minimally invasive approach. However, it may be very early to apply sentinel lymph node dissection and consequent intraoperative ESD for sentinel lymph node negative cases to become an accepted approach in clinical practice; this is because we still have a number of technical controversies to be resolved [23]. These include the accuracy of intraoperative pathological diagnosis, the necessity of full-thickness resection, and the possibility of cancer cells being present in afferent lymphatic vessels, leading to sentinel lymph nodes [23]. Further studies are required to verify the safety and effectiveness of combined treatment involving sentinel lymph node dissection and ESD.

In conclusion, long-term periodic endoscopy permits less invasive treatments and combinations of various treatments for effective GTC therapy. However, further investigations are required to establish a treatment strategy for lesions that do not fulfill the indications for endoscopic resection.

**Ethical Statement** We declare that our work conforms to the guidelines set forth in the Helsinki Declaration of 1975, as revised in 2000 and 2008, concerning Human and Animal Rights, and that we conformed with the policy concerning Informed Consent as shown on Springer.com (<http://www.springer.com/medicine/internal/journal/10388>).

**Conflict of interest** The authors declare that they have no conflicts of interest associated with this study.

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