Can we apply the same indication of endoscopic submucosal dissection for primary gastric cancer to remnant gastric cancer?

Yoon Young Choi · In Gyu Kwon · Sang Kil Lee · Hyun Ki Kim ·
Ji Yeong An · Hyoung Il Kim · Jae Ho Cheong · Richard Thomas Mliwa ·
Sung Kwan Shin · Yong Chan Lee · Woo Jin Hyung · Sung Hoon Noh

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Abstract

Background Currently, remnant gastric cancer (RGC) is uncommon compared with gastric stump cancer, but early detection of gastric cancer and improved postsurgical survival will lead to increased incidence of RGC. Therefore, the indication of endoscopic submucosal dissection (ESD) for RGC is now required, but there have been no reports about this because of the lack of information for RGC.

Methods A retrospective review was conducted on 105 patients who underwent completion total gastrectomy (CTG) and 5 patients who underwent ESD for RGC between January 1998 and December 2010 at Yonsei University Hospital.

Results Forty-one (39 %) of 105 patients were diagnosed with early RGC. Among these patients, 6 had an absolute

indication for ESD, whereas 11 met expanded criteria for ESD. In these patients, there was no association between the severity of the former gastric cancer and the current RGC. Also, none of these 17 patients had LN metastasis after CTG, and only 1 (2.4 %) of 41 early RGC patients had LN metastasis. Median operative time was 216 min for CTG and median hospital stay was 8 days. There were two major and five minor complications. One splenectomy was performed because of injury that occurred during CTG.

Conclusions Applying the indication of ESD for primary gastric cancer to RGC would be possible, and it could be an alternative treatment option for selected patients with RGC.

Keywords Remnant gastric cancer · Endoscopy · ESD · Lymph node · Gastric cancer

Y. Y. Choi and I. G. Kwon contributed equally to this work.

Y. Y. Choi · I. G. Kwon · J. Y. An · H. I. Kim · J. H. Cheong ·
R. T. Mliwa · W. J. Hyung · S. H. Noh (✉)
Department of Surgery, Yonsei University Health System,
Yonsei University College of Medicine, 134 Shinchon-dong,
Seodaemun-ku, Seoul 120-752, Republic of Korea
e-mail: sunghoonn@yuhs.ac

S. K. Lee · S. K. Shin · Y. C. Lee
Department of Gastroenterology, Yonsei University Health
System, Yonsei University College of Medicine, Seoul,
Republic of Korea

H. K. Kim
Department of Pathology, Yonsei University Health System,
Yonsei University College of Medicine, Seoul,
Republic of Korea

R. T. Mliwa
Department of Surgery, Muhimbili University of Health
and Allied Sciences, Dar es Salaam, Tanzania

Introduction

Early gastric cancer (EGC) is highly curable with endoscopic resection or surgery. Treatment of selected EGC cases using endoscopy was popularized in the late 1980s with the development of endoscopic mucosal resection (EMR) [1]. Endoscopic submucosal dissection (ESD) now permits complete resection for more larger and deeper tumors without piecemeal resection [2]. Consequently, ESD has extended the indications for endoscopic tumor resection in the absence of evidence for lymph node (LN) metastasis [3–5].

In contrast to endoscopic procedures, radical surgery permits evaluation of LN metastasis and has previously been considered to be the only method for achieving cure of remnant gastric cancer (RGC). However, adhesions and anatomic deformation resulting from a previous

gastrectomy with LN dissection increase the difficulty of the second operation, completion total gastrectomy (CTG) [6, 7]. In the absence of LN metastasis, ESD offers the possibility of cure without the risks associated with a second oncological surgical procedure. Even though ESD has already been used to treat carcinoma in the remnant stomach [8–10], to date, there has been no decided indication of ESD for RGC because it had been uncommon and, consequently, there has been no report that reviewed a large amount of pathological results for RGC after CTG.

Because early detection of gastric cancer and improved postsurgical survival will lead to an increased incidence of RGC, we now need to decide the indication of ESD for RGC. If the former gastric cancer (FGC) did not affect the current RGC, applying the indication of ESD for primary gastric cancer to RGC is possible. To inquire into the relationship between FGC with current RGC and the possibility of using the same indication of ESD for RGC, we reviewed the surgical and pathological outcomes of patients who underwent CTG for RGC, especially those who were possible candidates for ESD.

Patients and methods

We performed a retrospective review of the data of patients who underwent CTG for RGC between January 1998 and December 2010 at Yonsei University Hospital. In the same period of time, there were 9,984 cases of conventional gastric cancer patients. This review was approved by the Institutional Review Board of our institution (4-2012-0639).

Definitions

RGC was defined by the following criteria: (1) a history of curative gastrectomy for gastric adenocarcinoma, (2) an interval from curative gastrectomy to identification of remnant gastric tumor of more than 12 months, and (3) pathologically confirmed adenocarcinoma in the remnant stomach. When the depth of tumor was limited to the mucosa or submucosa layer and the tumor was RGC, we defined it as early RGC. In relative concept, gastric stump cancer (GSC) was defined by the criteria of a previous gastrectomy for a benign condition, followed by diagnosis of cancer in the remnant stomach. Papillary adenocarcinoma as well as well or moderately differentiated tubular adenocarcinoma was classified as differentiated type. Poorly differentiated tubular adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma were classified as undifferentiated types.

We applied the same indication of ESD for primary gastric cancer to RGC. An absolute indication (AI) for ESD

was defined by evidence of a non-ulcerative, differentiated-type lesion, limited to the gastric mucosa and <20 mm in maximal dimension. Expanded indication (EI) for ESD included (1) a non-ulcerative, differentiated tumor confined to the gastric mucosa irrespective of size, (2) an ulcerative, differentiated tumor confined to the gastric mucosa and <30 mm in maximal dimension, (3) a non-ulcerative, undifferentiated tumor confined to the gastric mucosa and <20 mm in maximal dimension, or (4) a differentiated tumor confined to the submucosa (sm1; <0.5 mm from the muscularis mucosa) and <30 mm in maximal dimension [11].

Investigated outcomes

We reviewed the characteristics of FGC, including the former tumor stage, type of surgical reconstruction, and interval between previous gastrectomy and CTG. We also investigated the characteristics of RGC, such as tumor location, tumor size, presence of ulcers, tumor histology, LN metastasis, and pathological T-stage. The operative time and in-patient hospitalization, treatment complications, patient survival, and disease recurrence following CTG were reviewed to inquire the postoperative outcomes. Procedural complications were divided into major and minor categories according to the necessity for interventional procedures.

Results

Characteristics of patients who underwent CTG for early RGC

In total, 105 patients underwent CTG for RGC, and among them, 41 (39 %) had early RGC. Six (14.6 %) of the 41 patients met the AI criteria for ESD, whereas 11 (26.8 %) met the EI criteria for ESD (Fig. 1). The median age of 17 patients who were possible candidates for ESD was 66 years (range 33–76 years), and 5 patients (29.4 %) were female. More than two-thirds (70.6 %) of patients had undergone previous Billroth II reconstruction procedures. Because 5 of the 17 patients who met ESD criteria underwent previous gastrectomy at other hospitals, the exact extent of previous LN dissection could not be determined. The stage of FGC varied from T1N0 to T4N1a. However, the exact tumor stage was unknown in 3 patients. The median interval from previous gastrectomy to CTG was 46 months (range 13–365 months; Table 1).

Among these possible candidates for ESD, RGC occurred at the anastomosis site in 7 patients (41.2 %). Six of these patients underwent Billroth II reconstruction (Tables 1, 2). There was no evidence of LN metastasis

Fig. 1 Characteristics of remnant gastric cancer (RGC). ESD endoscopic submucosal dissection

Table 1 Characteristics of former gastric cancer patients who met either an absolute indication or expanded indication for endoscopic submucosal dissection but underwent completion total gastrectomy (CTG)

Number of case	Age ^a	Sex	Reconstruction type	LN dissection	Stage	Interval to CTG (months)
AI for ESD						
1	45	M	DG with BII	D2	T1N0	17
2	71	M	DG with BII	D2	T3N1	33
3	66	M	DG with BII	–	– ^b	332
4	73	M	DG with BII	–	– ^b	341
5	76	M	DG with BII	D1+	T2N0	37
6	66	M	DG with BII	–	T1N0	20
EI for ESD						
7	70	M	DG with BII	D2	T3N1	59
8	52	M	DG with BII	D2	T1N0	112
9	40	M	DG with BI	D2	T1N0	25
10	68	M	DG with BII	–	– ^b	365
11	47	F	DG with BII	D1+	T1N0	13
12	74	M	DG with BII	D2	T3N0	26
13	63	M	DG with BI	D1+	T1N0	113
14	33	F	DG with BI	D2	T2N2	34
15	59	F	DG with BI	–	T1N0	46
16	43	F	DG with BII	D1+	T4N1	76
17	66	F	DG with BI	D2	T1N0	50

LN lymph node, CTG completion total gastrectomy, DG distal gastrectomy, BII Billroth II, BI Billroth I, ESD endoscopic submucosal dissection, AI absolute indication, EI expanded indication, M male, F female

^a Age at the time of CTG (years)

^b Failed to acquire information about pathological reports of previous operation

after CTG for RGC among these 17 patients. The duration of follow-up from CTG ranged from 18 to 98 months. One patient died of primary lung cancer, and follow-up was censored in 2 patients. Among the 41 patients diagnosed with early RGC, only 1 patient (2.4, 0–7.1 %) showed evidence of metastasis in 1 of 10 harvested LNs. The tumor in this patient invaded the submucosa (sm2, >0.5 mm from the muscularis mucosa); it measured 2.5 cm in length and was classified as a well-differentiated tubular adenocarcinoma (Table 3).

Postoperative outcomes after CTG for RGC

Table 4 shows the postoperative outcomes of CTG for RGC. The median operative time was 216 min, and the median hospital stay was 8 days. One patient underwent combined splenectomy during CTG because adhesiolysis caused injury to the spleen, and five patients experienced minor complications after CTG for RGC: three patients developed atelectasis, one developed anemia requiring transfusion with packed red blood cells, and one developed

Table 2 Characteristics of patients who met either an absolute indication or expanded indication for endoscopic submucosal dissection but underwent completion total gastrectomy

Number of case	Age ^b	Sex	T-stage	Histological type	Presence of ulcer	Size (mm)	Location	Lymph Node (positive LN/retrieved LN)	Duration of follow up (months)
AI for ESD									
1	45	M	m	Diff	–	≤20	NAS	0/6	145
2	71	M	m	Diff	–	≤20	NAS	0/11	79 ^a
3	66	M	m	Diff	–	≤20	Anastomosis site	0/19	81
4	73	M	m	Diff	–	≤20	Anastomosis site	0/13	24
5	76	M	m	Diff	–	≤20	Anastomosis site	0/8	30
6	66	M	m	Diff	–	≤20	NAS	0/1	24
EI for ESD									
7	70	M	m	Undiff	–	≤20	Anastomosis site	0/10	98 ^c
8	52	M	m	Undiff	–	≤20	NAS	0/0	73
9	40	M	m	Undiff	–	≤20	NAS	0/0	18
10	68	M	m	Diff	–	≤30	Anastomosis site	0/52	75 ^a
11	47	F	m	Undiff	–	≤20	NAS	0/2	18
12	74	M	m	Undiff	–	≤20	Anastomosis site	0/5	41
13	63	M	m	Undiff	–	≤20	Anastomosis site	0/11	35
14	33	F	m	Undiff	–	≤20	NAS	0/15	44
15	59	F	m	Undiff	–	≤20	NAS	0/8	24
16	43	F	m	Undiff	–	≤20	NAS	0/3	18
17	66	F	sm1	Diff	–	≤30	NAS	0/1	30

NAS non-anastomosis site, LN lymph node, AI absolute indication, EI expanded indication, ESD endoscopic submucosal dissection, M male, F female, m mucosa, sm submucosa, Diff differentiated type, Undiff undifferentiated type

^a Lost to follow-up at the indicated time

^b Age at the time of completion total gastrectomy (years)

^c The patient died secondary to sepsis following lung wedge resection for primary lung cancer

Table 3 Lymph node characteristics in patients who underwent completion total gastrectomy for early remnant gastric cancer

	pT-stage	Number of patients (LN + patients/total patients)	LN (positive LN/retrieved LN)
Early RGC (n = 41)	m	0/25	0/224
	sm	1 ^a /16 (6.3 %, 0–18.2 %)	1/120
	Total	1/41 (2.4 %, 0–7.1 %)	1/344

LN lymph node, RGC remnant gastric cancer, m mucosa, sm submucosa

^a A 2.5 × 2 cm tumor invading the submucosa (sm2, >0.5 mm from the muscularis mucosa): classified histologically as a well-differentiated tubular adenocarcinoma

an intraabdominal abscess, which required a change in intravenous antibiotics. One patient developed a pleural effusion and an intraabdominal abscess, which required external percutaneous drainage. One patient required reoperation because of leakage from the duodenal stump with A-loop obstruction and subsequently required admission to the intensive care unit.

Discussion

CTG for GSC is technically more challenging than total gastrectomy for primary gastric cancer because of the postoperative adhesions. However, because of previous extensive LN dissection, RGC is usually associated with more severe adhesions around the remnant stomach than GSC. Our results represented the difficulty of CTG for RGC: we identified five cases of minor complications and two cases of major complications, including reoperation, after CTG for RGC. Also, there was one combined splenectomy with CTG because of injury during the operation. Therefore, ESD prevents unnecessary complications and may be a better option if it applied with reasonable indication.

The present results showed that the severity of FGC was not associated with the interval to CTG or with survival after CTG for RGC. We also found no evidence of LN metastasis in patients who were candidates for ESD. In fact, the incidence of LN metastasis in early RGC was only 2.4 % (0–7.1 %) in our data, which is similar to the reported incidence of LN metastasis of 8.9 % (467 of 5,265

Table 4 Postoperative outcomes of completion total gastrectomy for remnant gastric cancer

	CTG (<i>n</i> = 17, range), [NAS (<i>n</i> = 10)]
OP time (min)	216 (125–300), [218 (145–290)]
Hospital stay (days)	8 (6–83), [9 (6–83)]
Complications	Minor Atelectasis: 3 (1 NAS, 2 anastomosis) Transfusion: 1 (NAS) ^a Intraabdominal abscess: 1 (NAS) Major Intraabdominal abscess with pleural effusion: 1 (NAS) ¹ Reoperation with intensive care unit care: 1 (NAS) Other Combined splenectomy resulting from injury

NAS non-anastomosis site, CTG completion total gastrectomy, OP operative

^a Both complications occurred in one patient

patients) in primary early gastric cancer [3]. This similarity between RGC and primary gastric cancer suggests that the LN metastasis of RGC is affected by current stage and not by the stage of the FGC. Previous studies that reported the prognosis of patients with RGC showed similar results. One report did not find evidence of LN metastasis in 9 patients with early RGC [12], and RGC itself was not associated with poor survival [13]; another report failed to identify a statistically significant difference in survival between RGC and GSC [14]. One study reported that the survival of patients with pT1 stage RGC was 76 % [15], a result worse than those of recent reports of survival from primary early gastric cancer, but this finding was based on data collected in the 1970s. Therefore, applying the indication of ESD for primary gastric cancer to RGC would be possible.

Despite the reported success of ESD for RGC or GSC [8, 16, 17], ESD is also technically challenging in the remnant stomach. Even when the patient has an entire stomach, difficulty with enfacement and access to the lesion can increase the frequency of hemorrhage during and after ESD if the lesion is located in the upper third of the stomach [18]. In the case of the remnant stomach, the narrow space and fibrotic change around the anastomosis site increase the difficulty of ESD.

Others have hypothesized that use of staples may complicate ESD when RGC arises on a stapled anastomosis site. There have been a few reports about ESD for gastric cancer on a stapler site: one case report described successful ESD of a gastric tube cancer that arose on a previous surgical staple line [19], and another suggested that en bloc ESD can be highly effective, despite the presence

of staples, when performed by an experienced endoscopist [8]. These reports could support the technical possibility of ESD for RGC on a stapler site, but the technical feasibility of ESD for RGC on an anastomosis site, a stapler site, should be carefully considered. In addition, the accuracy of preoperative endoscopic ultrasound was reported as 75 %, and even for T1 stage was only 77 % [20]. It would be more difficult to estimate the real depth of tumor invasion than primary gastric cancer if the tumor is located on the anastomosis site, especially for a staple site. Thus, the accuracy of preoperative diagnosis would decrease for tumors on the anastomosis site and might be even worse for a stapler site. For these reasons it would be better not to select ESD when the tumor is located on an anastomosis site, especially on a stapler site.

We believe that early detection and advances in treatment for primary gastric cancer suggest that the incidence of RGC will gradually increase. Prior studies have suggested a role for ESD in the setting of RGC or GSC [8, 16, 17]. However, to the best of our knowledge, ours is the first study to review the pathological results of RGC with the incidence of LN metastasis. In fact, the critical aspect of this study is the limited number of cases: there were only 17 cases of possible candidates of ESD for RGC. This limitation would be resolved by future individual patient data meta-analysis or prospective multicenter studies, which will offer additional information and concrete evidence regarding the indications of ESD for RGC.

Conclusions

The present results showed the possibility to apply the indications of ESD for primary gastric cancer to RGC. Thus, ESD could be an alternative treatment option for selected patients with RGC. A future multicenter study or systematic review is required to decide the indications of ESD for RGC with more concrete evidence.

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Conflict of interest None.

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