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切除不能進行再発胃癌に対する新たな免疫化学療法の開発

藤原　義之*

要旨　切除不能進行再発胃癌に対する現時点の推奨される治療法は，2010年10月に改訂された胃癌治療ガイドラインに記載があるとおりS-1+シスプラチンによる抗癌剤治療である。しかし，その治療成績は，生存期間中央値で13ヶ月と，不十分であることはいうまでもない。我々は，S-1+シスプラチン療法に腫瘍新生血管をターゲットとしたペプチドワクチン治療を併用する新たな治療法の開発をめざし，第Ⅰ,Ⅱ相臨床試験を施行した。具体的には，Vascular endothelial growth factor receptors（VEGF-R1, R2）の2種類のペプチドをHLA-A2402の患者には，併用し，それ以外は，S-1+シスプラチン療法のみを施行した。予定登録数30症例を登録し，安全性および有効性の検討を行った。安全性に関しては，ワクチン併用による重篤な有害事象の出現は認めなかった。有効性に関しては，今後の検討となるが，ペプチドワクチンによる特異的免疫反応が，抗癌剤併用でも確認されており期待が持てる。

Ⅰ．はじめに

切除不能進行再発胃癌に対する標準治療は，我国で施行された「手術不能又は再発胃癌に対するTS-1単独療法/TS-1+cisplatin（CDDP）併用療法による比較試験：SPIRITS trial」の結果により，TS-1+CDDP併用療法である[1]。本年10月に改訂された胃癌治療ガイドラインにも，「胃癌に対する初回治療として現時点で推奨されるのはS-1+CDDPである」という記載が追加されている[2]。しかし，抗癌剤治療は，耐性の出現，有害事象による継続困難等の問題があり，この推奨治療でさえ，無増悪生存期間中央値6ヶ月，全生存期間中央値13ヶ月であり，新規治療法の開発が急務である。

近年，分子標的治療薬が次々と開発されており，胃癌に対しても，抗癌剤と併用することで予後改善が報告されている。ToGA trialでは，HER2陽性胃癌に対し，5-FU系抗癌剤＋CDDP療法にHER2抗体であるtrastuzumab（Herceptin）を併用することで予後が改善することを証明し，胃癌において初めて分子標的治療の有用性を示した[3]。AVAGAST trialでは，5-FU系抗

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癌剤であるcapecitabine+CDDPに抗VEGF抗体であるbevacizumabを併用することで，残念ながら生存期間の延長効果は示せなかったが，無増悪生存期間の延長効果を示した[1]。我々は，標準治療であるS-1+CDDP療法に腫瘍新生血管に特異的に発現するVEGF receptor 1とreceptor2を標的とするペプチドワクチン療法を併用する臨床試験（第Ⅰ，Ⅱ相試験）を施行し，進行再発胃癌に対する新規治療法の開発を試みたのでここに途中経過を報告する。

Ⅱ．対象と方法

対象は切除不能進行胃癌あるいは，再発胃癌とした。適格基準および除外基準を表1に示す。適格基準はSPIRITS trialに準じた。

表1　適格基準と除外基準

Ⅰ．適格基準
1）組織診によって胃癌である。
2）StageⅣの非切除症例あるいは再発胃癌。
3）ECOGのPerformance statusが0～1。
4）年齢　20歳以上74歳以下。
5）主要臓器の機能が保持されている。
6）試験開始日より3ヶ月以上生存すると予想される。
7）RECISTによる計測可能病変の有無は問わないが，腫瘍臨床効果の判定が可能である。
8）前治療から4週間以上が経過している。
9）原疾患に対するTS-1による治療歴がない。
10）経口摂取が可能。
11）患者本人の同意を文書で得られること。

Ⅱ．除外基準
1）重篤な合併症を有する症例（コントロール困難な糖尿病，肝障害，心疾患，出血等）
2）妊婦（本臨床研究開始後は妊娠可能な女性は避妊する）。
3）授乳中の女性（本臨床研究開始後は授乳を中止する）。
4）妊娠の意思のある患者（試験期間中は男女共に適切な避妊をする）。
5）制御困難な活動性感染症がある。
6）試験中に以下の薬剤を投与する必要性がある患者。腎ステロイド剤の全身投与又は免疫抑制剤の全身投与
7）制御されていない重複癌を有する。
8）治癒に至っていない外傷性病変を有する。
9）腸管麻痺あるいは間質性肺炎が疑われる。
10）医師，責任医師が不適切と認める。

本試験の目的は，主要目的：安全性，Time to Progression（TTP），副次的目的：免疫学的評価，抗腫瘍効果，治療完遂率，生存期間中央値とした。

試験の概略を図1，図2に示す。患者登録を行い，VEGFR1，R2ペプチドワクチンは，HLA-A2402拘束性であるので，HLA-Aがマッチする場合は，S-1+CDDP療法に加え，週1回ペプチドワクチンをGMP gradeのIncomplete Freund's Adjuvant, MONTANIDE（SEPPIC社，France）1 mlと混和し皮内あるいは皮下注を施行した。HLA型のミスマッチ例は，S-1+CDDP療法のみ施行し同様に経過観察を行った。ペプチドワクチン接種に関しては，S-1+CDDP療法が終了後も患者の希望があれば継続した。

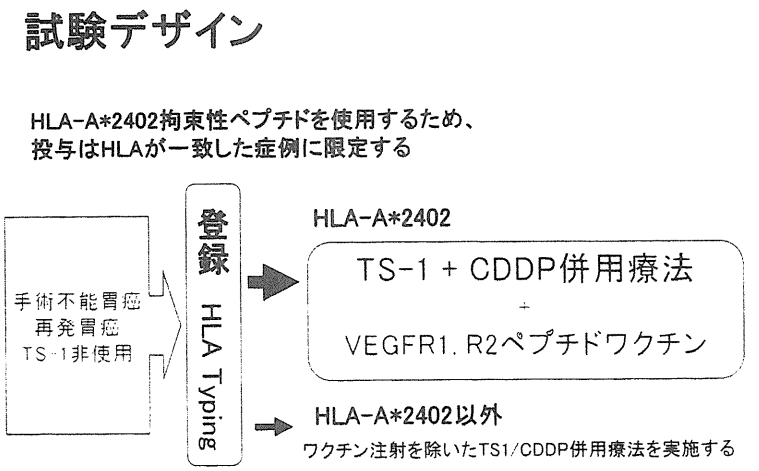

図1　試験デザイン

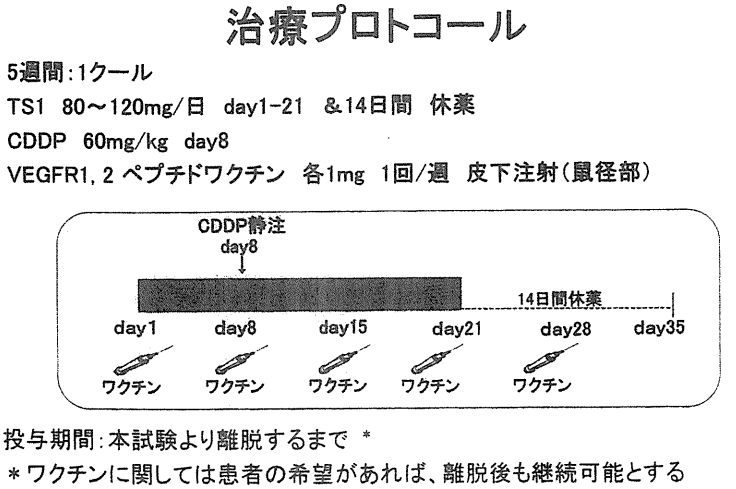

図2　治療プロトコール

Ⅲ. 結　果

2007年11月から2010年３月までに目標である30症例を登録した。現時点で平均観察期間は１年10か月である。表２に患者背景を示す。男女比は，25対５，切除不能進行か再発かは，23対７であった。HLA-A2402でペプチドワクチンを併用した症例は22例，HLA型が合わず抗癌剤治療のみを施行した症例が８例であった。表３に，２サイクル終了までの有害事象を示す。ワクチンを併用しても特に重篤な有害事象の増加はなく，注射局所反応として２例に皮膚潰瘍を認めたが，治療中断することはなく継続可能であった。表４に全症例の治療成績を示す。全奏効率は50%で，平均cycle数は6.4サイクル（１～18）であった。表５に，ワクチン併用の有無別に治療成績を示した。２サイクル後の奏効率は，ワクチン併用群で55%，非併用で38%であった。２サイクル後の病勢コントロール率は，ワクチン群で100%，非ワクチン群で63%であった。ワクチン投与22例中12例の患者血清を用い，ペプチド特異的な細胞障害性Ｔリンパ球の誘導を調べたところ，７例（58%）に強い反応性を示すCD8陽性Ｔリンパ球の誘導を確認できた（図３）。予後に関しては，現在経過観察中であるが，ワクチン併用群でTTP中央値9.6か月，生存期間中央値14.2か月であった。

表２　患者背景

登録数		30
年齢（中央値）		61+-10.5
性	男/女	25/5
切除不能/再発		23/7
組織型	分化/未分化	11/19
HLA型	A-2402/それ以外	22/8

表３　安全性評価（２サイクル終了時点）

	ワクチン群	非ワクチン群	SPIRITS
症例数	22	8	148
骨髄系（G3,4）			
白血球減少	3（14%）	0	12%
好中球減少	5（23%）	0	40%
赤血球減少	4（18%）	4（50%）	26%
血小板減少	2（9%）	2（25%）	5%
非骨髄（G2,3）			
T-BIL上昇	1（5%）	0	
Cr上昇	0	0	
ALB低下	8（36%）	5（63%）	
嘔気嘔吐	1（5%）	3（38%）	
下痢	2（9%）	0	
口内炎	1（5%）	0	
発熱	3（14%）	2（25%）	
皮膚潰瘍	2（9%）		

表4　治療成績1

登録数		30
2サイクル完遂率		28(93%)
奏効率	PR/SD/PD	15/12/3
		50%
病勢コントロール率		27(90%)
平均サイクル数		6.4(1~18)

表5　治療成績2

	ワクチン群	非ワクチン群
登録数	22	8
2サイクル完遂率	21(95%)	7(88%)
奏効率(2サイクル後)		
PR/SD/PD	12/10/0	3/2/3
	12(55%)	3(38%)
病勢コントロール率		
2サイクル後	22(100%)	5(63%)
4サイクル後	18(82%)	5(63%)
6サイクル後	14(64%)	4(50%)

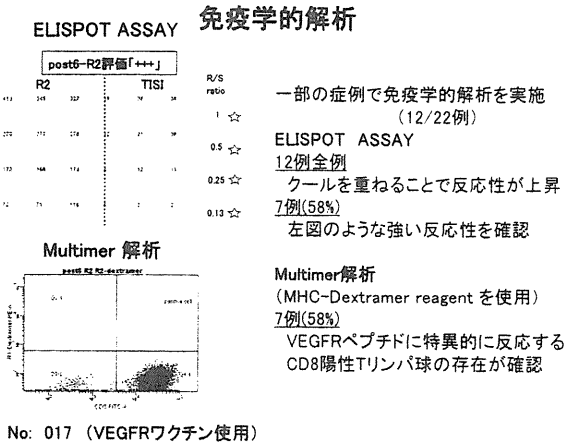

図3　免疫学的解析

Ⅳ. 考　察

近年，細胞傷害性T細胞（CTL）によって認識・傷害される腫瘍抗原が発見され，その後，腫瘍特異的抗原が次々と同定され，これを標的とする特異的免疫療法であるエピトープペプチドを用いたがんワクチン療法の臨床試験が進行中である。本研究は，ワクチン療法によるCTLの標的細胞を腫瘍細胞自身ではなく腫瘍新生血管とし，腫瘍新生血管由来分子（VFGF-R1, -R2）を標的としたワクチン療法を，胃癌の標準的化学療法に併用する臨床試験である。

VEGFR1及びVEGFR2は，乳癌，大腸癌，腎癌，悪性黒色腫，肺癌など多くの固形腫瘍の腫瘍新生血管内皮細胞に高発現しており，それぞれ，腫瘍新生血管の構築，及び，腫瘍血管内皮細胞の増殖と遊走に関与している[5)6)]。またVEGFR2の発現が，癌細胞の増殖と強く関連していることも明らかになっている[7)8)]。

ヒトにおける基礎的解析の結果，VEGFR1 および VEGFR2 を認識し傷害する CTL クローンが存在することを証明し，強力な CTL を誘導できる HLA-A*2402 拘束性のエピトープペプチドが同定され，癌患者末梢血からも CTL を誘導できたことにより，CTL 前駆体細胞が癌患者においても存在することが明らかになった[9)-11)]。以上より，本ペプチドを投与し，患者に VEGFR1 および VEGFR2 特異的 CTL を誘導することで，腫瘍血管新生を阻害することによる抗腫瘍効果を得る可能性がある。

今回，抗癌剤と併用することの安全性は，検証できた。さらに，抗癌剤との併用においても特異的免疫反応の誘導が確認されたことは，重要な情報である。治療効果については，さらなる臨床試験が必要であり今後の研究が待たれる。

V．おわりに

本研究では，進行再発胃癌に対し，現時点の推奨治療である S-1+CDDP 療法に血管新生制御を目的としたペプチドワクチン療法を併用することの安全性と有効性を検証した。ワクチン治療を併用することの安全性が確認され，ワクチン特異的な免疫反応の誘導も確認することができた。今後大規模試験により有効性の検討が望まれる。

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World Journal of Surgery

Minimally Invasive Surgery for Gastric Cancer: The Future Standard of Care

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Abstract Laparoscopy-assisted distal gastrectomy for gastric cancer was first reported by Kitano et al. in 1991. Laparoscopic wedge resection (LWR) and intragastric mucosal resection (IGMR) were quickly adapted for gastric cancer limited to the mucosal layer and having no risk of lymph node metastasis. Following improvements in endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), the use of LWR and IGMR for these indications decreased, and patients with gastric cancer, including those with a risk of lymph node metastases, were more likely to be managed with laparoscopic gastrectomy (LG) with lymph node dissection. Many retrospective comparative trials and randomized-controlled trials (RCT) have confirmed that LG is safe and feasible, and that short-term outcomes are better than those of open gastrectomy (OG) in patients with early gastric cancer (EGC). However, these trials did not include a satisfactory number of patients to establish clinical evidence. Thus, additional multicenter randomized-controlled trials are needed to delineate significantly quantifiable differences between LG and OG. As laparoscopic experience has accumulated, the indications for LG have been broadened to include older and overweight patients and those with advanced gastric cancer. Moreover, advanced techniques, such as laparoscopy-assisted total gastrectomy, laparoscopy-assisted proximal gastrectomy, laparoscopy-assisted pylorus-preserving gastrectomy (PPG), and extended lymph node dissection (D2) have been widely performed.

In the near future, sentinel node navigation and robotic surgery will become additional options in minimally invasive surgery (MIS) involving LG. Such developments will improve the quality of life of patients following gastric cancer surgery.

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Introduction

Interest in the various aspects of minimally invasive surgery (MIS) rapidly increased following the first report of laparoscopic cholecystectomy in 1989 [1]. Controversy has surrounded whether MIS in cancer patients is comparable to open surgery in terms of oncological adequacy and safety. Minimally invasive surgery has several advantages compared with conventional open surgery, such as less invasiveness and pain, speedier recovery, and better cosmetic results. As surgeons became more experienced in this area and developments continued in laparoscopic surgical instruments, MIS began to be used as curative therapy in cancer patients [2].

In 1994, Kitano et al. presented the first report of laparoscopy-assisted distal gastrectomy for gastric cancer [3]. In 1994, Ohgami et al. reported the first use of laparoscopic wedge resection (LWR) for the treatment of early gastric cancer (EGC) [4]. In LWR, surgeons use an approach to perform a full-thickness resection of the stomach wall with organ preservation. Intragastric mucosal resection (IGMR) enabled mucosal resections of any part of the stomach except the anterior wall [5]. In the beginning, the indications for LWR and IGMR were strictly limited to mucosal gastric cancer with no risk of lymph node metastasis. Minimally invasive surgery for gastric cancer employs function-preserving procedures using either endoscopy or laparoscopy. The use of LWR and IGMR for mucosal cancer appeared to decline following developments in endoscopic mucosal resection (EMR) and endoscopic

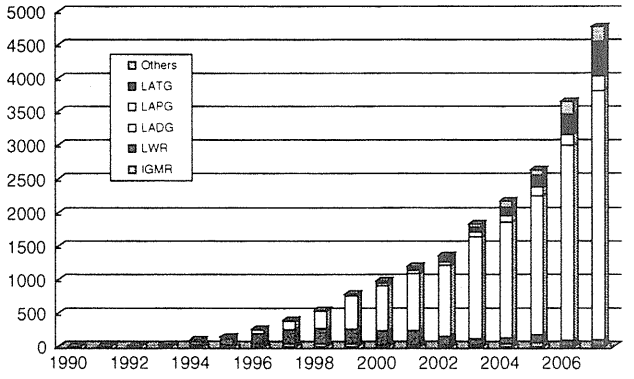

Fig. 1 The numbers of laparoscopic gastrectomies for gastric cancer in Japan [6]. *LATG* laparoscopy-assisted total gastrectomy; *LAPG* laparoscopy-assisted proximal gastrectomy; *LADG* laparoscopy-assisted distal gastrectomy; *LWR* laparoscopic wedge resection; *IGMR* intragastric mucosal resection

submucosal dissection (ESD). However, laparoscopic gastrectomy (LG) has continued to be used, even in early gastric cancer (EGC) patients with a potential risk of lymph node metastasis. This is particularly true in Japan where there is a high prevalence of EGC (Fig. 1) [6]. As laparoscopic techniques and surgical instruments have improved, interest in advanced approaches has grown, among them, extended lymph node dissection and total gastrectomy [7–9]. Multicenter prospective randomized clinical trials to compare short- and long-term outcomes in laparoscopic surgery and open surgery are underway in Korea [10] and Japan. This review summarizes past and current trends in MIS for gastric cancer.

Indications for the use of LG

From EGC to advanced gastric cancer (AGC)

Initially, laparoscopic gastrectomy (LG) was indicated only for EGC patients with a low risk of lymph node metastasis. The Japanese Gastric Cancer Association proposed a clinical guideline for the treatment of gastric cancer in Japan in 2001; the guideline was revised in 2004 [11, 12]. Based on those recommendations, LG is recommended for gastric cancer patients with a preoperative stage Ia (cT1N0M0) diagnosis; patients with stage Ib (cT1N1M0 and cT2N0M0) disease are referred for EMR or ESD. The preoperative stage is determined by endoscopy, endoscopic ultrasound, and abdominal computed tomography. Although a number of institutes adhere to the guideline, LG has also been referred to as a pre-established technique that is still under clinical investigation due to the uncertain quality of lymph node dissection and the lack of long-term data.

The Japanese Gastric Cancer Association's guideline recognizes three types of laparoscopic lymph node dissection: perigastric lymph node dissection (D1 + α), additional lymph node dissection along the common hepatic artery (D1 + β), and extended lymph node dissection (D2). In relation to EGC, the association recommends three optimal lymph node dissection levels. It advocates D1 + α for mucosal cancer not indicated for EMR and for differentiated submucosal cancers less than 1.5 cm in diameter. It recommends D1 + β for submucosal cancer without preoperatively determined lymph node metastasis and for EGC tumors less than 2.0 cm in diameter or with preoperatively determined perigastric lymph node metastasis. The guideline recommends D2 for EGC tumors greater than 2.0 cm in diameter with N1 metastasis; D2 is also approved for advanced gastric cancer (AGC).

A large randomized-controlled European trial failed to prove the efficacy of open gastrectomy (OG) with D2 lymph node dissection due to a high morbidity and mortality rate [13]. However, OG with D2 lymph node dissection is routinely performed for AGC in Asian countries. D2 lymph node dissection has been considered difficult to perform laparoscopically. If an experienced laparoscopic surgeon performs the operation using the standardized procedure, D2 lymph node dissection can be carried out successfully [14]. There have been many recent reports of institutions successfully performing LG with D2 lymph node dissection for AGC and improving both short- and long-term outcomes [6–8, 15–18].

The impact of obesity on LG

Overweight patients are generally thought to have a greater risk of potential complications and require more technically difficult operations than normal weight patients. In OG, obesity is not a risk factor for the survival of patients with gastric cancer, although it is independently predictive of postoperative complications [19]. Various technical disadvantages of LG for obese patients have been reported, including reduced surgical visibility, blood oozing from soft tissues, a dissection plane hindered by adipose tissue, and difficulty with anastomosis. Noshiro et al. previously reported that LG for obese patients resulted in longer operative times, delayed recovery of bowel activity, and a greater rate of extension of the mini-laparotomy incision or conversion to laparotomy [20]. However, other reports have suggested that obesity may not increase operative morbidity following LG for gastric cancer [21–26]. Nevertheless, when a surgeon is relatively inexperienced in the area of LG, a careful approach is required, particularly for male patients with a high body mass index (BMI) [26].

The impact of age on LG

The number of elderly people with gastric cancer has continued to increase, despite the fact that the total number of patients with this type of cancer has reached a plateau [27]. Previous studies have shown that elderly patients who undergo OG tend to have increased morbidity and mortality rates and long hospital stays as a result of co-morbid conditions and decreased functional reserve [28–30]. Minimally invasive surgery may offer substantial advantages to this population in terms of fewer cardiorespiratory complications, shorter hospital stays, and a speedier return to physical activities. Many reports have concluded that LG is a feasible and safe procedure in elderly patients if the patients have been selected carefully and the procedure has been performed by an experienced surgeon [31–36].

Functional preservation in LG

Some institutions have performed laparoscopic proximal gastrectomy for EGC located in the proximal third of the stomach [37, 38]. Partial (distal or proximal), rather than total, gastrectomy was performed due to a previous report of an association between total gastrectomy and significant weight loss caused by insufficient dietary intake [39]. This study also reported that the long-term prognosis of patients who underwent total gastrectomy was significantly worse than that for those who underwent partial gastrectomy.

Pylorus-preserving gastrectomy (PPG) was originally a treatment option for patients with gastric ulcers [40]. However, the procedure is now mostly restricted to patients with EGC located in the distal two-thirds of the stomach [41]. Pylorus-preserving gastrectomy is considered superior to distal gastrectomy followed by Billroth I reconstruction because it largely eliminates postoperative dumping syndrome and the duodenal juice reflux. Following the establishment of laparoscopy-assisted PPG (LAPPG), this procedure has been used in many institutions, especially in Japan and Korea [42, 43]. The selection of LAPPG versus PPG is due to the low incidence of postoperative stasis and adequate lymph node retrieval [44].

Efficacy of LG versus OG in MIS

Retrospective comparative trials

A large number of retrospective comparative trials have compared LG with OG (Table 1) [45–61]. Although most of these trials have been conducted in Japan, many recent studies have been performed in Western countries. In 2000, Adachi et al. reported a comparative study of LG versus OG [45]. They concluded that laparoscopy-assisted distal gastrectomy (LADG) has several advantages over open distal gastrectomy (ODG) for EGC, such as less surgical trauma, fewer instances of impaired nutrition, reduced postoperative pain, rapid return of gastrointestinal function, shorter hospital stays, and no reduction in curability. In another study, the researchers compared laparoscopy-assisted total gastrectomy (LATG) with conventional open total gastrectomy (OTG) [55]. They reported that LATG was successful in 20 patients and that there was no significant difference in operating time between the two groups. However, blood loss was smaller in the LATG group compared with the OTG group. The time to ambulatory status, first flatus, and first oral intake were significantly shorter in the LATG group, as was the length of the postoperative hospital stay. The frequency of analgesics given in the LATG group was lower than that in the OTG group. The authors concluded that LATG is suitable and feasible for EGC and that it has the advantage of a shorter recovery time compared with OTG. Hiki et al. compared LAPPG and conventional PPG (CPPG) with respect to the quality of lymph node dissection and other clinical outcomes [56]. The operative times for the LAPPG procedure (274 ± 6 min) were significantly longer than for the CPPG procedures (259 ± 8 min; $P = 0.047$), although the estimated blood loss with LAPPG (153 ± 13 mL) was not significantly less than that with CPPG (184 ± 13 mL; $p = 0.13$). The incidence of postoperative complications was comparable between the two groups. Postoperative gastric fullness was the most frequent complication in both groups. Analgesics were required 3 days after the operation, and the time to analgesia was shorter in patients who underwent LAPPG. The time to first flatus and start of oral intake was reduced in the LAPPG group compared with the CPPG group; the length of the postoperative hospital stay was also shorter. There was no significant difference between the procedures in terms of the number of lymph nodes retrieved from any of the nodal stations. The authors concluded that clinical outcomes of surgical treatment were comparable between LAPPG and CPPG in terms of station-dependent lymph node dissection. Overall, the intraoperative findings revealed significant differences in terms of operative time and intraoperative blood loss in the LG group. In relation to short-term outcomes, the LG group experienced less postoperative pain, fewer instances of postoperative morbidity, lower mortality rates, and shorter hospital stays. These findings suggest that LG may be considered as MIS for gastric cancer.

Postoperative complications after LG

Concerns remain that the complexity of the LG procedure may increase the rate of unexpected complications.

Table 1 Retrospective comparative trials comparing laparoscopic gastrectomy (LG) and open gastrectomy (OG) (>20 patients in each group)

Study (year)	Type of gastrectomy	No. of patients	Operative time, min	Blood loss, ml	Conversion to OG (%)	No. of resected LN	Morbidity, %	Mortality, %	Hospital stay, days	References
Adachi et al. (2000)	LADG/ODG	49/53	246/228	158/302[a]	0	15/19	8/21	0/0	18/23[a]	[45]
Shimizu et al. (2000)	LADG/ODG	21/31	299/212[a]	273/350	4.8	14/18	19/13	0/0	29/41	[46]
Yano et al. (2001)	LADG/ODG	24/35	220/210	108/296[a]	0	19/24	4/11	0/0	21/29[a]	[48]
Tanimura et al. (2003)	LADG/ODG	160/100	232/184[a]	121/469[a]	–	31/30	–	0/0	12/23[a]	[51]
Naka et al. (2005)	LADG/ODG	20/22	289/145[a]	106/261[a]	0	10/12	–	0/0	18/26[a]	[52]
Noshiro et al. (2005)	LADG/ODG	37/31	320/277[a]	163/488[a]	0	43/41	5/13	0/0	14/20[a]	[53]
Kim et al. (2005)	LADG/ODG	71/76	250/181[a]	–	2.8	23/27[a]	17/17	1.4/1.3	9/11[a]	[54]
Hiki et al. (2006)	LAPPG/CPPG	72/37	279/259[a]	153/184	0	32/29	28/38	0/0	18/29[a]	[56]
Lee et al. (2006)	LADG/ODG	136/120	158/150[a]	49/126[a]	0	31/40[a]	8/12.5	0/0.8	8/11	[58]
Ikenaga et al. (2006)	LADG/ODG	47/33	273/218[a]	167/196	0	37/43	–	–	–	[59]
Strong et al. (2009)	LDG/ODG	30/30	270/126[a]	200/150	–	–	26/43	0/0	5/7[a]	[60]
Orsenigo et al. (2010)	LAG/OG	109/269	272/230[a]	170/372[a]	15.6	31/27[a]	26/19.3[a]	2/1.4	13/15	[61]

LADG laparoscopy-assisted distal gastrectomy, *ODG* open distal gastrectomy, *LAPPG* laparoscopy-assisted pylorus-preserving gastrectomy, *CPPG* conventional pylorus-preserving gastrectomy, *LDG* laparoscopic distal gastrectomy, *LAG* laparoscopy-assisted gastrectomy, *OG* open gastrectomy

[a] Statistically significant

According to a nationwide survey conducted by the Japanese Society for Endoscopic Surgery in 2008 [6], the incidence of intraoperative and postoperative complications with LADG were 1.7% and 8.2%, respectively; in LATG, they were 2.7% and 17.8%, respectively. The rates of conversions to open surgery were 1.3% with LADG and 2.1% with LATG. The most common intraoperative and postoperative complications were bleeding and anastomotic-related problems (leakage, stricture, and stasis). The results suggest that the complication rate is gradually decreasing and that it has reached a plateau in LADG. However, problems remain with LATG, especially in relation to the anastomotic technique. In another study, Park et al. retrospectively reviewed postoperative complications in 300 consecutive patients who had undergone LG for gastric cancer [62]. They reported that 20.3% suffered postoperative complications, including wound infection (7%), anastomotic-related problems (5.3%), and bleeding (4%). The 30-day mortality rate was 0.7%. They concluded that LG could be performed with acceptable perioperative complication rates and that both the surgeon's experience and careful patient selection determined optimal patient outcomes. Kunisaki et al. analyzed predictive factors for surgical complications of LG in terms of BMI and visceral fat area (VFA) [63]. In 152 patients, the conversion to open surgery for uncontrollable bleeding was 5.9% (9/152); postoperative complications were 6.9% (7/101) among males and 1.9% (1/51) among females. The study indicated that a high BMI and greater VFA independently predicted the conversion to open surgery and postoperative complications. The authors emphasized that caution should be exercised in relation to the use of LG to prevent surgical complications in men with a high VFA. Obama et al. compared surgical outcomes in 138 consecutive patients with gastric cancer who had undergone LG with peripancreatic lymphadenectomy with outcomes in 95 consecutive OG cases [64]. The overall postoperative morbidity rates were 15% in the LG group and 20% in the OG group. The rates of grade B and C postoperative pancreatic fistula (criteria of the International Study Group on Pancreatic Fistula) were 7% in the LG group and 2% in the OG group, with no statistical difference. The authors stressed that care must be taken not to damage the pancreas when performing LG with peripancreatic lymphadenectomy.

Table 2 Long-term outcomes after LG for gastric cancer

Study (year)	Kitano et al. [65] (2007)	Hwang et al. [66] (2009)	Song et al. [68] (2010)	Lee et al. [69] (2010)
No. of patients	1,294	197	1,485	601
Period	1994–2003	1998–2007	1998–2005	2000–2009
Indication	EGC	EGC, cT2N0M0	EGC, AGC	EGC, cT2N0-1M0
Median follow-up, months	36	45	41	35.9
Survival rate				
Stage				
Ia	99.8	100	98.6	94.2
Ib	98.7	96.4	–	87.4
IIa	85.7	87.5	86.0	80.8
IIb	–	–	–	69.6
IIIa	–	16.7	44.7	–
IIIb	–	100	–	–
IV	–	100	50.0	–

EGC early gastric cancer, *AGC* advance gastric cancer

Long-term outcomes

Although there is solid evidence on the short-term efficacy of LG for EGC, there is little information on the procedure's long-term efficacy. In 2007, the Japanese Laparoscopic Surgery Study Group reported a multicenter study of oncological outcomes following LG for EGC in Japan [65]. Of 1,294 patients who underwent LG, the 5-year disease-free survival rate was 99.8% in stage IA, 98.7% in stage IB, and 85.7% in stage II with a median follow-up of 36 months. In a single-center study of 197 patients who underwent LG, Hwang et al. reported that the actual 3-year disease-free survival rates for EGC and AGC were 98.8% and 79.1%, respectively [66]. Lee et al. analyzed long-term outcomes in 106 patients who underwent LG with pathological confirmation of AGC [67]. They reported 32 total gastrectomies and 74 distal gastrectomies with D2 lymphadenectomy. The overall and disease-free survival rates were 81.4% and 72.4%, respectively, with a median follow-up of 21.5 months. Song et al. reviewed a retrospective multicenter study (Korean Laparoscopic Gastrointestinal Surgery Study Group) to assess the timing and patterns of disease recurrence [68]. In a 41-month follow-up, the incidence of disease recurrence was 1.6% in patients with EGC and 13.4% in patients with AGC. Advanced T-classification and lymph node metastasis were risk factors for disease recurrence. The authors concluded that LG showed satisfactory long-term oncological outcomes similar to those of OG. In a single-center study, Lee et al. reported on the long-term oncological outcomes of 601 patients who underwent LG [69]. They recommended that LG should be used for all gastric cancers up to preoperative stage T2N1. In patients of stage IA, the 5-year overall and disease-free survival rates were 94.2% and 89.9%, respectively. In patients with stage IB disease, they were 87.4% and 82.7%, respectively; in stage IIA, they were 80.8% and 70.7%, respectively; and in stage IIB, they were 69.6% and 63.1%, respectively. The authors suggested that LG for EGC is acceptable in terms of surgical quality, as well as long-term oncological outcomes; hence, it should be considered as the primary treatment in patients with EGC (Table 2).

Randomized controlled trial (RCT) comparing LG with OG

To date, seven randomized controlled trials have compared LG with OG for gastric cancer. In all the trials, LADG was compared with ODG (Table 3) [10, 70–75]. Six of the trials enrolled only patients with clinically diagnosed EGC. One of the trials reported a 5-year follow-up of 59 patients with EGC or AGC; 29 of the patients underwent open subtotal gastrectomy, and 30 patients underwent laparoscopic resection [70]. The authors found that the LG group experienced a longer operative duration, decreased blood loss, shorter time to resumption of oral intake, and earlier discharge from hospital. The mean numbers of resected lymph nodes were approximately the same in both groups. Postoperative mortality rates were 6.7% and 3.3% in the OG and LG group, respectively. The morbidity rate in the OG group was 27.6% and 26.7% in the LG group. Five-year overall and disease-free survival rates were 55.7% and 54.8%, respectively, in the OG group and 58.9% and 57.3%, respectively, in the LG group. None of the parameters studied were significantly different between groups. The authors concluded that laparoscopic radical subtotal gastrectomy for distal gastric cancer is a feasible and safe oncological procedure supported by short- and

Table 3 Randomized control trials comparing LG and OG

Study (year)	Type of gastrectomy	Indication	No. of patients	Operative time, min	Blood loss, ml	Conversion to OG, %	No. of resected LN	Morbidity, %	Mortality, %	Hospital stay, days	Reference
Kitano et al. (2002)	LADG/ ODG	EGC	14/14	227/171[a]	117/ 258[a]	0	20/25	14/29	0/0	18/16	[71]
Fujii et al. (2003)	LADG/ ODG	EGC	10/10	226/180[a]	134/206	0	–	20/20	0/0	–	[72]
Hayashi et al. (2005)	LADG/ ODG	EGC	14/14	378/235[a]	327/ 489[a]	0	28/27	22/57	0/0	12/18[a]	[73]
Huscher et al. (2005)	LADG/ ODG	EGC, AGC	30/29	196/168	229/ 391[a]	0	30/33	23/28	3/6	10/15[a]	[70]
Lee et al. (2005)	LADG/ ODG	EGC	24/23	319/190[a]	336/294	0	32/38	13/43	0/0	11/17	[74]
Kim et al. (2008)	LADG/ ODG	EGC	82/82	252/171[a]	112/ 267[a]	1.2	39/45[a]	0/5	0/0	7/9[a]	[75]
Kim et al. (2008)	LADG/ ODG	EGC	179/161	–	109/ 200[a]	0	–	12/15	1.1/0	–	[10]
Meta-analysis											
Chen et al. (2009)	LADG/ ODG	EGC	323/306	MD 86.6[a]	MD – 108.3[a]	–	MD –4.8	RR 0.61[a]	RD 0.01	MD –2.0[a]	[76]

LN lymph nodes, *MD* mean difference, *RR* risk ratio, *RD* risk difference

[a] Statistically significant

long-term results similar to those obtained with an open surgery. Chen et al. reported a meta-analysis of the six trials of LG and OG in patients (629) with a clinical diagnosis of EGC [76]. Comparing LADG with ODG, less postoperative early morbidity (risk ratio = 0.61; $P = 0.01$), similar mortality (risk difference = 0.01; $P = 0.32$), prolonged operative time (mean difference [MD] = 86.64 min; $P < 0.00001$), decreased intraoperative blood loss (MD = −108.33 ml; $P = 0.001$), decreased numbers of dissected lymph nodes (MD = −4.88; $P < 0.00001$), forward time to oral intake (MD = −0.48 d; $P = 0.32$), and shortened hospital stays (MD = −2.03 d; $P = 0.14$). The authors concluded that LADG could offer EGC patients a slight benefit in terms of decreased intraoperative blood loss and postoperative morbidity rates; however, it could also increase the operative time and decrease the number of dissected lymph nodes.

Large multicenter randomized controlled trials are still required to delineate significantly quantifiable differences between LG and OG. The KLASS Trial of 342 patients so far has demonstrated reduced morbidity and mortality [10]. However, this trial is ongoing and has yet to determine whether there is a difference in overall survival between the two groups. Currently, the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group is conducting a multi-institutional prospective randomized controlled phase III trial (JCOG 0912). This study has been registered with Japan's University Hospital Medical Information Network (UMIN) Clinical Trial Registry (number: UMIN000003319). Separate phase III studies of LG for AGC are also underway to evaluate perspectives on the role of LG in MIS.

Perspectives of LG—pursuing a more minimally invasive surgery

Other investigations of LG have been reported in the context of improving patients' quality of life (QOL). Yamada et al. investigated the efficacy of preserving the celiac branch of the vagus nerve following LADG [77]. They concluded that preservation of the celiac branch of the vagus nerve was associated with a decrease in dumping syndrome and residual foods in the remnant stomach.

Totally laparoscopic gastrectomy represents the final step in the evolution of laparoscopy-assisted gastrectomy. In their review, Katsios et al. noted that modern totally laparoscopic gastrectomy is the most promising approach for improving the short-term QOL of patients with resectable gastric cancer [78]. One of the main advantages of totally laparoscopic gastrectomy is the reduction in the length of the surgical incision. The smaller incision lowers the risk of postoperative infection, hernia, and pain. The technical complexities of intracorporeal reconstruction also impinge on totally laparoscopic gastrectomy. In a report on operative techniques in intracorporeal reconstruction

following laparoscopic distal gastrectomy (LDG), Kanaya et al. described a method for Billroth I anastomosis after LDG that employs only endoscopic linear staplers [79]. In another study, Takaori et al. described the use of intracorporeal Roux-en-Y anastomosis with linear staplers in which gastrojejunostomy was carried out by "functional end-to-end anastomosis" between the residual stomach and the jejunum [80]. Ikeda et al. reported a retrospective analysis aimed at determining the potential advantages of totally laparoscopic distal gastrectomy (TLDG): 24 patients underwent LADG and 56 patients underwent TLDG [81]. Mean blood loss was significantly lower in the TLDG group than in the LADG group. The patients in the TLDG group also recovered earlier and, thus, they had a significantly shorter postoperative hospital stay. The authors concluded that TLDG has several advantages compared with LADG, including small wound size, less invasiveness, secure ablation, and safe anastomosis, and that these advantages are independent of the patient's constitution and the cancer site.

A new treatment concept has been introduced for EGC based on the location and pathological findings of sentinel lymph nodes (SN). In the near future, laparoscopic wedge resection for SN-negative superficial gastric cancer will be an option, in addition to MIS [82, 83]. A combination of ESD and SN mapping is another potential option for superficial cancer; this less-invasive approach would improve patients' QOL in terms of preserving the whole stomach [84].

Robotic surgery may also begin to be exploited alongside conventional laparoscopic surgery. The technical feasibility, effectiveness, and safety of robot-assisted gastrectomy with lymphadenectomy using the da Vinci system have already been demonstrated [85, 86]. The use of robotics offers the surgeon improved dexterity, with an internal articulated endoscopic "wrist" that allows 7 degrees of freedom, including tremor filtering, motion scaling, and stereoscopic vision. In Asian countries, da Vinci robot systems have already been introduced, and a number of leading hospitals have incorporated the da Vinci system in LG with lymph node dissection over a period of time.

Conclusions

Since its introduction in 1991, the importance of laparoscopic gastrectomy for MIS in gastric cancer has been recognized worldwide. The use of LG is expected to grow with continuous innovative developments. However, before LG can be adopted for use in a greater range of clinical applications, several issues need to be resolved. In particular, attention needs to focus on patients with serosa-positive gastric cancer. The results of ongoing RCTs will shed light on the utility of laparoscopic gastrectomy in the next 10 years. We believe that laparoscopic gastrectomy represents an important type of MIS that can maximize patients' QOL following gastric cancer surgery.

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症 例

PTX/CDDPを用いた化学放射線療法とS-1投与によりCRが認められている食道胃接合部癌の1例

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A Case of Advanced Adenocarcinoma of Esophagogastric Junction with Severe Esophageal Invasion Effectively Treated by Chemoradiotherapy Using Paclitaxel and Cisplatin, and S-1 after Chemoradiotherapy: Hisataka Fujiwara[*1], Keisuke Koeda[*1], Masafumi Konosu[*1], Nobuyuki Hosoi[*1], Yoshiyuki Tamasawa[*2], Masahiro Sase[*2], Tomonori Tsukahara[*3], Akira Ushio[*3], Masami Taguchi[*4] and Go Wakabayashi[*1] (*[1]*Dept. of Surgery, Iwate Medical University,* *[2]*Dept. of Surgery,* *[3]*Dept. of Gastroenterology, and* *[4]*Dept. of Radiology, Hachinohe Red Cross Hospital*)

Summary

The patient was a 66-year-old male with adenocarcinoma of the esophagogastric junction and severe esophageal invasion, which was diagnosed as cType 3, cT4a (SE) cN3cM1 (LYM), cStage Ⅳ (histopathology: por 1). We tried concurrent chemoradiotherapy consisting of PTX 60 mg/m^2 and CDDP 25 mg/m^2, respectively (once a week), and a total of 45 Gy of radiotherapy treatment. Then, for effective continuation, chemotherapy using S-1 was performed as second-line therapy. A complete response was achieved and continued for more than 2 years after initial chemoradiotherapy; his complaints abated and his quality of life improved. Although gastro-intestinal symptoms and bone marrow suppression were observed as adverse effects, they were within a tolerable range and did not interfere with the concurrent chemoradiotherapy. This regimen appears to be feasible and effective for advanced gastric carcinoma refractory to other regimens. **Key words**: Chemoradiotherapy, Paclitaxel, Gastric cancer (*Received Dec. 6, 2010/Accepted Feb. 9, 2011*)

要旨 症例は66歳，男性。臨床診断は，食道胃接合部癌〔cType 3，por 1，cT4a (SE)，cN3，cM1 (LYM)，cP0，cH0，cStage Ⅳ〕であった。本症例に対して化学放射線療法（化学療法: PTX 60 mg/m^{2}およびCDDP 25 mg/m^{2}の同時各週投与を4回，放射線照射: 下部食道と胃上部に1.8 Gyを20回，下部食道のみ1.8 Gyを5回）を開始した。治療終了後の効果判定では総合効果PRの腫瘍縮小効果（原発巣の平坦化および縮小，LN縮小率57%）が認められ，本治療後はS-1単独投与にて外来通院治療へ移行した。化学放射線療法終了後2か月後の内視鏡所見では原発巣は消失かつ瘢痕化しており，生検でも癌細胞は認められなかった。CTではリンパ節転移巣が消失しており最良総合効果CRと判定した。S-1投与は1年間継続され以後は中止となった。最終治療より1年間経過した現在も病状増悪徴候は認められていない。本療法施行中の有害事象はすべてgrade 2以下であり，有害事象による治療休止は経験しなかった。本療法は切除不能進行胃癌に対して臨床的有用性の高い化学放射線療法の一つであると思われた。

はじめに

胸部下部食道浸潤を伴う食道胃接合部癌に対して化学放射線療法とS-1を逐次施行した結果，長期完全奏効を認めた症例を経験したので報告する。

Ⅰ．症 例

患者: 66歳，男性。

主訴: 嚥下困難。

既往歴: 40歳 アルコール性肝障害。60歳 じん肺。65

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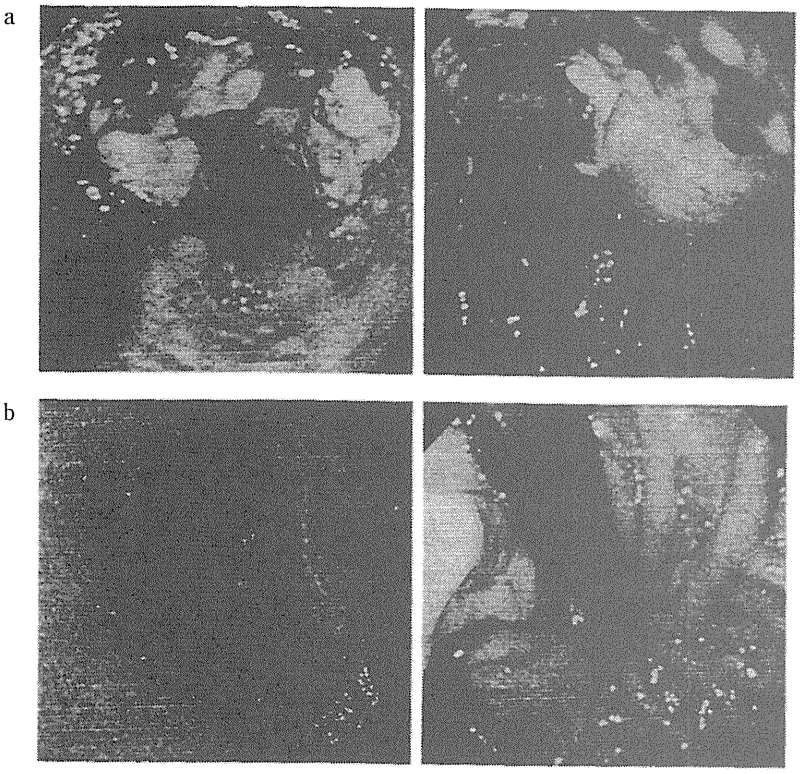

Fig. 1 Upper gastrointestinal endoscopy
a: Endoscopic examination revealed a type 3 cancer mainly located in esophagogastric junction with severe esophagus invasion.
b: Two month later after chemoradiotherapy, the lesion was disappeared and a normal mucosa was reproduced.

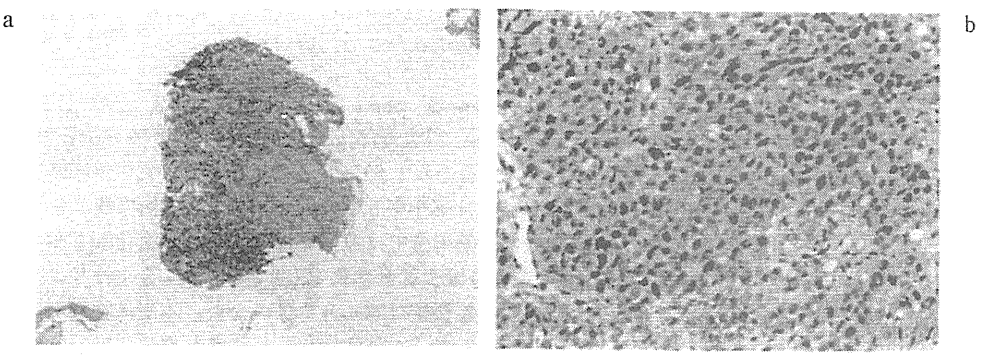

Fig. 2 Microscopic examination
a: HE（×4・Original magnification）.
b: HE（×40・Original magnification）.

歳 MALT リンパ腫（除菌および放射線治療）。

現病歴: 2008 年 7 月ごろより食事摂取時の嚥下困難を自覚。症状増悪し経口摂取困難となり，8 月に当院消化器科受診。精査・加療目的に入院となった。

入院時身体所見: 身長 165 cm，体重 55 kg。PS 0。

入院時検査所見: 血液一般，血液生化学所見，CEA および CA19-9 は基準値範囲内であった。

画像所見: 上部消化管内視鏡検査にて噴門部に Borrmann 3 型の腫瘍および約 6 cm の食道浸潤が認められ，fiber 通過に難渋した（Fig. 1a）。病理組織学的検査では充実型低分化腺癌の診断であった（Fig. 2）。腹部 CT 検査では，噴門部より胸部下部食道へ連続する壁肥厚と No. 7，11p，16a1 のリンパ節腫大が認められた（Fig. 3a）。臨床診断は，食道胃接合部癌，cType 3，cT4a（SE），cN3，cM1（LYM），cP0，cH0，cStage Ⅳ[1]。

治療経過: 当初，緩和手術を考慮したが本人および家族からの手術に関する同意は得られなかった。最終的に，高橋ら[2]の報告を基に原発巣に対する早期縮小効果を期待し化学放射線療法の方針とした。化学療法に関しては PTX および CDDP の同時毎週投与を計 4 回〔PTX（60 mg/m^2）を 5% glucose 250 mL で 60 分点滴静注後，CDDP（25 mg/m^2）を生食 500 mL で 60 分点滴静注〕，

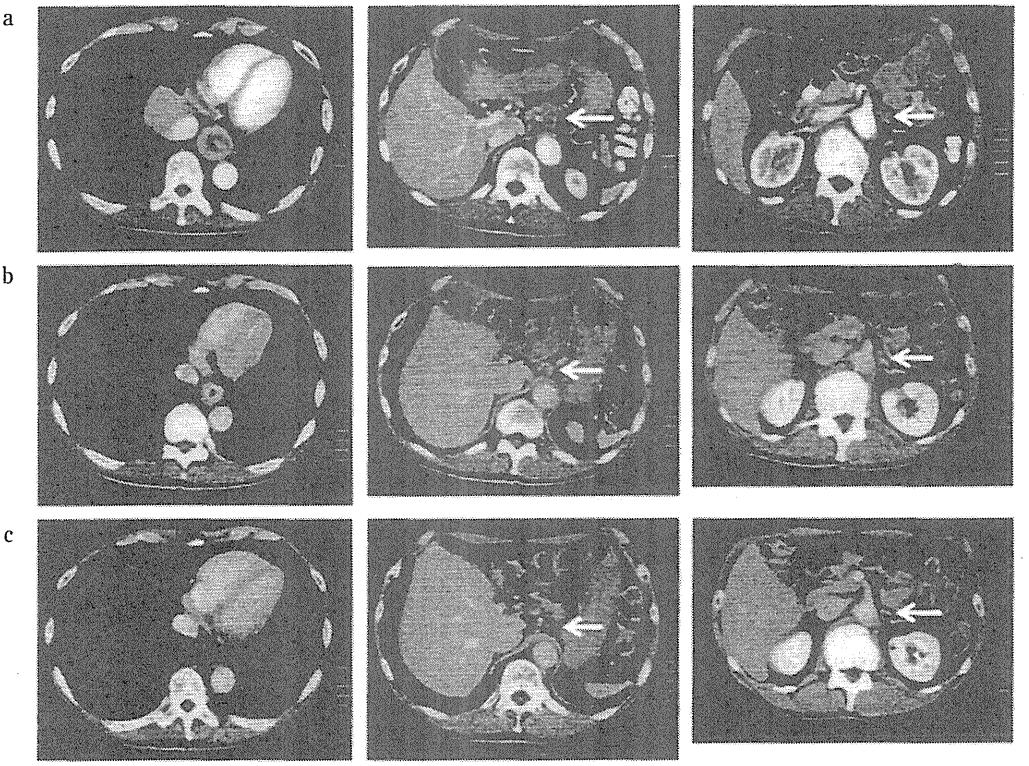

Fig. 3　Enhanced computed tomography (CT) axial image
a: CT revealed wall thickness of the esophagus, and enlarged lympho node.
b: Just after chemoradiotherapy, these lesions were redused.
c: Two month later after chemoradiotherapy, these lesions were disappeared or changed a normal size.

放射線治療についてはMALTリンパ腫治療に際して胃全体に30 Gyを照射した治療歴があることから，胸部下部食道から噴門部を中心とした胃上部に1.8 Gy/回で計20回，その後下部食道のみに1.8 Gy/回で計5回，計45 Gyを照射予定とした。治療開始後2週間経過した時点の評価では原発巣・転移巣ともに増大傾向を認めず，さらに自覚症状改善も得られていることより治療継続とした。化学放射線療法終了後約1週間おいて効果判定を行ったところ，上部消化管内視鏡検査では腫瘍周堤の平坦化と潰瘍底の消失を認め，食道浸潤部分においても地図状潰瘍の散在を認めるのみであった。さらに，生検では癌細胞は認められず，Group 1の診断であった。CTでは，原発巣の壁肥厚は著明に改善しており，リンパ節転移巣の腫瘍縮小率は57%とPRの腫瘍縮小効果が認められ（Fig. 3b），また，新病変の出現を認めなかった[1]。自覚症状では嚥下困難はほぼ消失し粥食を十分量摂取可能となり，治療終了後約2週間後に退院とした。有害事象としては，血液毒性ではgrade 2の好中球減少，grade 1の白血球減少と貧血を認め，非血液毒性ではgrade 1の疲労感および嘔気が認められたのみで，治療休止となることはなかった[3]。

化学放射線療法終了後の方針としてはPTXおよびCDDPの同時投与を基本とした外来化学療法を続ける予定であった。しかし，患者側より治療継続と職場復帰の両立を図りたいこと，遠方からの通院のため時間的余裕がないこと，治療費が比較的高額となることなどからPTXおよびCDDPによる治療継続困難の訴えがあり，2008年10月よりS-1（80 mg/m^2，4週投与2週休薬）を開始した。外来治療開始2か月後に効果判定を行ったところ，上部消化管内視鏡検査では原発巣の瘢痕化を認めるのみであり，生検による確認でも前回と同様にGroup 1の診断であった（Fig. 1b）。また，CT検査ではリンパ節腫大の消失が認められており（Fig. 3c），その後，約2か月ごとのCTによる治療効果判定においても病状増悪および新病変出現は認められないことから，最良総合効果CRと判断した[1]。約12か月間のCR持続を確認したところで，患者希望にてS-1投与を終了した。S-1中止後は無治療にて約12か月間経過したが病状増悪を認めておらず，今後も外来経過観察予定である。

Ⅱ．考　察

米国では胃癌・食道胃接合部癌における治癒切除後の化学放射線療法は標準治療であり[4]，術前化学放射線療法は第Ⅱ相試験として報告されている[5]。一方，手術による局所制御が確立している本邦では，おおむね姑息的治療の一つとして認識されており，Stage Ⅳ症例におけ