OS and RFS at 5 years in patients with stage II or III gastric cancer who underwent D2 gastrectomy. Postoperative chemotherapy with S-1 can be recommended for patients with stage II or III gastric cancer who undergo D2 gastrectomy, at least in Asian populations.

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特集 Stage Ⅳ胃癌における外科治療の有用性

切除不能 stage Ⅳ進行胃癌に対する化学療法後の手術成績

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Evaluation of the Effectiveness of Surgery in Incurable Gastric Cancer Cases after Chemotherapy: Mihara Y[*1], Kochi M[*1], Fujii M[*1], Kanamori N[*1], Kaiga T[*1], Hagiwara K[*1], Funada T[*1], Tamegai H[*1], Watanabe M[*1] and Takayama T[*1] ([*1]Department of Digestive Surgery, Nihon University School of Medicine)

We retrospectively evaluated 86 patients with incurable gastric cancer. These patients were divided into chemotherapy alone group (n=59) and operation after chemotherapy group (n=27). The median survival time (MST) in the operation group and chemotherapy alone group were 21.3 and 11.3 months, respectively ($P \leq 0.001$). The operation group was further divided into 2 subgroups depending on whether the patients underwent curative or non-curative resection. The MST in the curative resection (n=16) group and non-curative resection (n=11) group were 35.6 and 16.2 months, respectively ($P \leq 0.005$). The main cause of non-curative resection was peritoneal metastasis. There was no significant difference between the MST in the non-curative resection group and that in the chemotherapy alone group. Our results suggest that curative resection after chemotherapy provides better survival benefit in incurable gastric cancer patients.

Staging laparoscopy may be useful for planning surgery after chemotherapy in patients with incurable gastric cancer.

Key words: Incurable gastric cancer, Chemotherapy, Curative resection

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はじめに

現在胃癌の術前化学療法は，切除可能な進行胃癌に対し down staging による根治性の向上を目指したものと，切除不能進行胃癌に化学療法が奏効し，結果的に切除可能となったものとに大きく2つに分けられる．前者の regimen は一般的に S-1/CDDP が用いられ，1～2クール施行後の切除が一般的であるが[1,2]，後者に関してはその regimen や施行クール数は確立されたものはなく，切除可能となるまで継続するのが現状である．

今回われわれは他臓器浸潤（T4），第3群リンパ節転移（N3），肝転移（H1），腹膜転移（P1），腹腔洗浄細胞診（CY1），遠隔転移陽性（M1）の因子の存在により，根治度 A,B が見込めない「切除不能 stage Ⅳ進行胃癌」に対する化学療法後の手術成績を，化学療法単独群と比較検討した．

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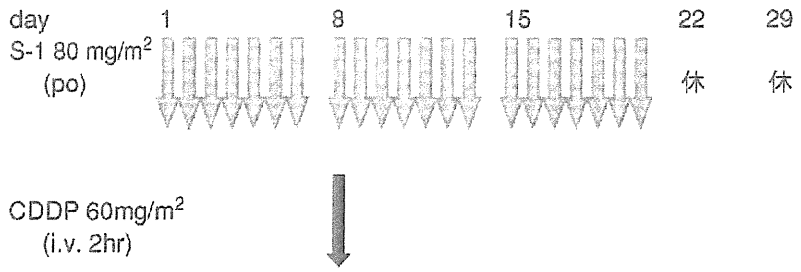

図1　化学療法の Regimen

1 対象と方法

1) 対　象

検索対象は，当院における2008年3月より2009年8月までの化学療法を施行した初発の切除不能胃癌86例で，化学療法単独施行群59例と化学療法施行後手術施行群27例に分け比較検討，手術施行群をさらに根治切除施行群16例，非根治切除施行群11例に分けて，比較検討をした．

2) 手術適応

切除不能進行胃癌に対する化学療法後に手術適応と判断した条件は1）遠隔リンパ節転移が画像上消失している，2）肝転移は画像上消失し，3カ月以上出現を認めない，3）腹膜転移が画像上腹水の出現が6カ月以上認めない．の3条件のいずれか認めた場合を手術適応条件とした．

3) 化学療法

Regimen は S-1/CDDP を施行した．S-1 80 mg/m^2 を3週間内服し，CDDP を day 8 に 60 mg/m^2 で点滴加療し，その後2週間休薬とした（図1）．2コース以上施行後内視鏡で原発巣の残存を確認後，4週間休薬後手術を施行した．

4) 検定方法

また2群間のデータ比較は student's t 検定または Mann-Whitney 検定，カイ二乗検定を用い，生存期間解析は Kaplan-Meier 法より行った．また $P<0.05$ を有意差ありとした．

表1　患者背景1

		n=86（%）
性	男性	67(77.9)
	女性	19(22.1)
年齢	中央値［Range］	65［30～84］
占拠部位	上部	15(17.4)
	中部	41(47.7)
	下部	30(34.9)
切除不能因子	N	28(32.6)
	P	16(18.6)
	H	16(18.6)
	SI	13(15.1)
	M	13(15.1)
化学療法	中央値［Range］	5［2～14］
奏効率	CR	1
	PR	44
		52.3%

2 結　果

患者背景を表1（全症例），表2（化学療法単独施行群，化学療法施行後手術施行群），表3（根治切除群，非根治切除群）に示した．化学療法単独群と化学療法施行後手術施行群及び根治切除群と非根治切除群の2群間の患者背景は共に有意差を認めなかった．

切除不能の要因は全体でリンパ節転移28例（32.6%），腹膜転移16例（18.6%），肝転移16例（18.6%），他臓器浸潤13例（15.1%），遠隔転移13例（15.1%）であった．化学療法の施行クールは中央値は5クール［2～14］であった．

また手術施行群27例の術式は胃全摘11例，幽門側胃切除術5例，胃空腸吻合術11例，単開腹1例で，化学療法後根治切除症例は16例（根治切除率59.3%）であった．また非根治切除

表2　患者背景2

		化学療法群 n=59 (%)	手術群 n=27 (%)	P
性	男性	48(81.4)	19(70.4%)	0.62
	女性	11(18.6)	8(29.6)	
年齢	中央値 [Range]	65[34~84]	63 [30~79]	0.74
占拠部位	上部	9(15.3)	6(22.2)	0.12
	中部	30(50.8)	11(40.7)	
	下部	20(33.9)	10(37.0)	
切除不能因子	N	15(25.4)	13(48.1)	0.08
	P	11(18.6)	5(18.5)	
	H	14(23.7)	2(7.4)	
	SI	6(10.2)	7(25.9)	
	M	13(22.0)	0(0)	
化学療法	中央値 [Range]	5 [2~14]	5 [2~8]	0.28
奏効率	CR	0	1	
	PR	18	26	
		30.5%	100%	

表3　患者背景3

		手術根治群 n=16 (%)	手術非根治群 n=11 (%)	P
性	男性	10(62.5)	9(81.8)	0.43
	女性	6(37.5)	2(1.8)	
年齢	中央値 [Range]	63 [38~79]	63 [30~79]	0.87
占拠部位	上部	2(12.5)	0(0)	0.05
	中部	7(43.8)	3(27.3)	
	下部	7(43.8)	8(72.7)	
切除不能因子	N	10(62.5)	3(27.3)	0.05
	P	2(12.5)	4(36.4)	
	H	1(6.3)	2(1.8)	
	SI	3(1.9)	2(1.8)	
	M	0(0)	0(0)	
化学療法	中央値 [Range]	5 [2~5]	5 [2~8]	0.82
奏効率	CR	1	0	
	PR	15	11	
		100%	100%	

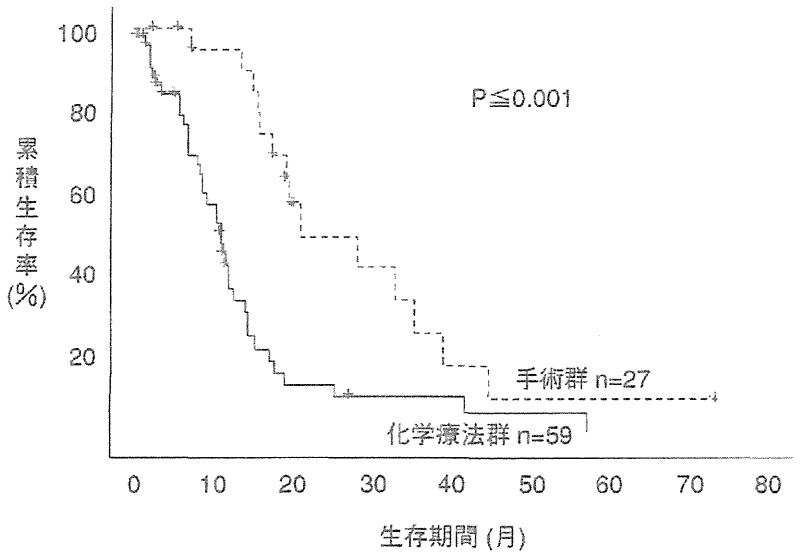

図2　化学療法群 vs 手術群の累積生存率

(11例) となった要因の内訳は，腹膜転移6例，他臓器浸潤3例，肝転移1例，リンパ節転移1例で，切除不能の要因は，腹膜転移が最も多かった (55%)．

化学療法単独群 (59例) と，化学療法後手術施行群 (27例)，生存率を比較すると，Median Survival Time (MST) は，11.3カ月 vs 21.3カ月と有意に，手術施行群が良好であった (P=0.001) (図2)．手術施行群の根治切除群 (16例) と非根治切除群 (11例) の生存率を比較すると，MSTは35.6カ月 vs 16.2カ月と有意差に根治切除群が良好であった (P=0.005) (図3)．化学療法単独群 (59例) と化学療法後非根治切除群 (11例) の生存率の比較を行ったところ，MSTは11.3カ月 vs 16.2カ月 (P=0.09) で両群間に有意差は認めなかった (図4)．

3 考　察

当科の根治切除不能 Stage Ⅳ 胃癌の化学療法後の手術施行例は化学療法単独群に比べ良好な治療成績であったが，化学療法後手術施行群の

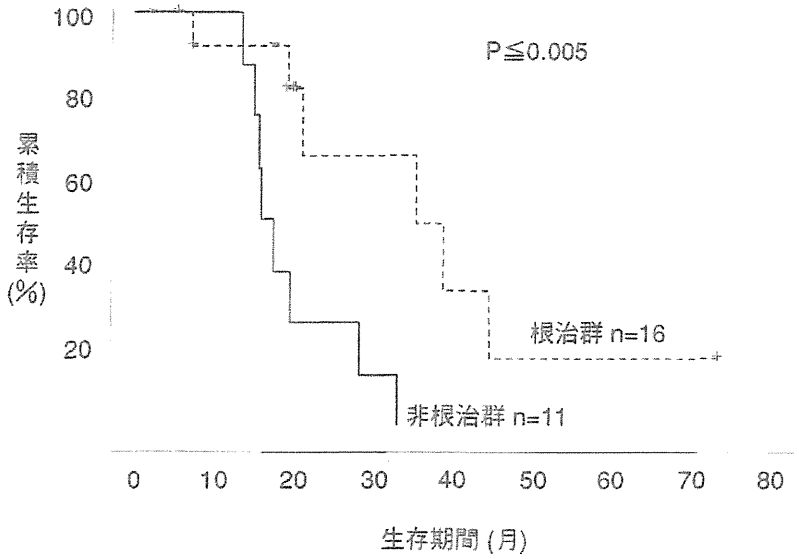

図3　化学療法＋手術根治群 vs 化学療法＋手術非根治群の累積生存率

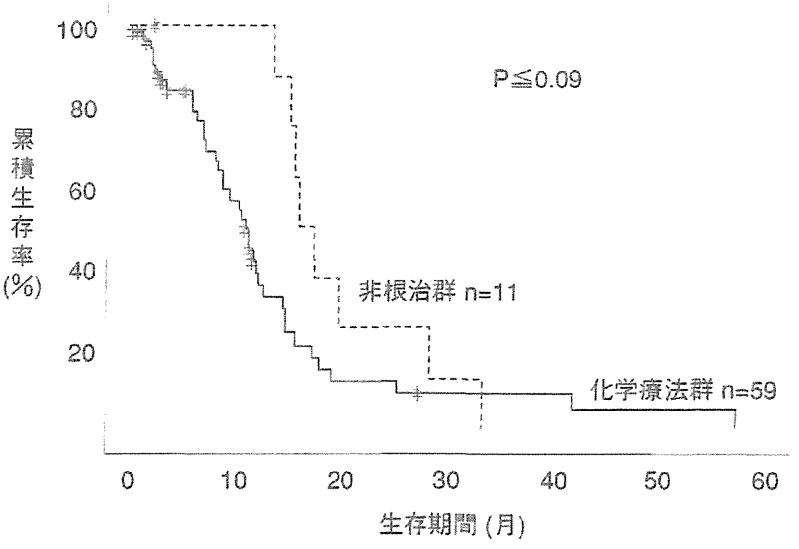

図4　化学療法 vs 化学療法＋手術非根治群の累積生存率

MST が良好であった要因は，手術施行群中に根治切除が多く含まれるためと考えられた．これは根治切除群と非根治切除群の MST の比較において根治切除群で有意差があったことと，化学療法群と非根治切除群の MST で有意差を認めなかった結果より，姑息的手術や減量手術といった非根治切除術には予後改善の影響力がないことが推測され，切除不能進行胃癌においては，化学療法後の根治切除が，長期予後を得る条件であることが示唆された．

岡部らは根治切除不能胃癌で手術先行群（134例），化学療法先行手術施行群（55例）の比較検討をしているが，いずれも治癒切除例が非治癒切除例より生存曲線において有意に良好であると報告している[3]．

本検証では非根治切除の要因として腹膜転移が多かったため，術前検査として P 因子や CY 因子の存在の有無の検索目的に，術前審査腹腔鏡検査を施行し，非根治切除因子の有無を明らかにした上で手術適応を決定する必要があると考えた．

今回の化学療法の regimen は S-1/CDDP のみであった．これは JCOG9912 試験と SPIRITS trial の結果により，5-FU に対する S-1 の非劣性と，S-1/CDDP 併用療法が S-1 単独療法の全生

存において勝ることが示されたことに基づいており，そのため現状わが国における切除不能再発胃癌の化学療法の第一選択はS-1/CDDPとなっていることによる[4,5]．しかし腎不全でS-1やCDDPが使用不可能な場合もあり，さらに現在ToGA trial等の結果が示すように，分子標的治療薬を含め，他の有効なregimenが出現する可能性があるため，今後他のregimenでの解析が必要であると考えられた[6]．

まとめ

切除不能stage Ⅳ進行胃癌に対する化学療法後の手術治療は，根治手術が求められると考えられた．非根治切除の最大の原因が腹膜転移であったことから，これらの手術治療の決定には術前審査腹腔鏡検査の必要性が考えられた．

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A Case of Complete Response to S-1 plus CDDP in Early-Stage Mucosal Esophageal Cancer

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Abstract. *We report a case of early-stage mucosal esophageal cancer, showing a complete response to S-1 and cis-diamminedichloplatinum (CDDP). The patient was a 67-year-old man with synchronous double primary early-stage mucosal esophageal and advanced gastric cancer. We planned neoadjuvant chemotherapy with S-1 and CDDP for the advanced gastric cancer and endoscopic mucosal resection for the early-stage esophageal cancer. After the first course of chemotherapy, the endoscopy revealed that the esophageal cancer had become a normal mucosal lesion, and the biopsy was negative for cancer. We diagnosed a complete response to S-1 and CDDP in early-stage esophageal cancer. After two courses of chemotherapy, distal gastrectomy was performed. The patient is still alive with no sign of recurrence at 16 months after the disappearance of the original tumor. These results suggest that chemotherapy with S-1 plus CDDP may be effective in early-stage esophageal cancer.*

The standard treatment for early-stage esophageal cancer is esophagectomy (1, 2). Despite advances in endoscopic therapy, the prognosis of early-stage mucosal esophageal cancer is still poor (3, 4). Several prospective trials have demonstrated that neoadjuvant chemotherapy, in conjunction with surgical intervention, confers a survival benefit for locally advanced esophageal cancer (5, 6). Tumor response to chemotherapy in early-stage esophageal cancer, however, remains to be elucidated. Complete remission of early-stage esophageal cancer with preoperative chemotherapy is rare. One such case is reported here.

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Key Words: Early-stage esophageal cancer, S-1 plus CDDP, complete response.

Case Report

The patient was a 67-year-old man who had previously consulted his home doctor with atrial fibrillation. In January 2009, the patient was referred to the Department of Digestive Surgery, Nihon University School of Medicine, Itabashi Hospital, with esophageal and gastric tumors which were identified during a follow-up examination. Upper gastrointestinal endoscopy revealed a mid-esophageal type IIc tumor measuring 2.0 cm×1.5 cm (Figure 1a) and a type 2 tumor in the lower stomach, measuring 3.5 cm×3.5 cm (Figure 2). Biopsy specimens revealed that the esophageal tumor was a well differentiated squamous cell carcinoma and the stomach tumor was a poorly differentiated adenocarcinoma. We diagnosed synchronous double primary early-stage mucosal esophageal and advanced gastric cancer. Computed tomography, revealed multiple lymph node metastases around the stomach (Figure 3). Neoadjuvant chemotherapy with S-1 (Taiho Pharmaceutical, Tokyo, Japan) and cis-diamminedichloroplatinum (CDDP) was carried out for the advanced gastric cancer and endscopic mucosal resection was planned for the early-stage esophageal cancer. S-1 was administered orally, at a dose of 80 mg/m^2 per day, for 21 days. Infusional CDDP was administered at a dose of 90 mg/m^2 for 90 minutes on day 8. The patient developed grade 3 diarrhoea during the first course, which resolved spontaneously after the discontinuation of chemotherapy. After the first course of chemotherapy, endoscopy was performed with the aim of carrying out endoscopic mucosal resection. However, the endoscopy revealed that the esophageal cancer had become a normal mucosal lesion (Figure 1b), and the biopsy was negative for cancer. We diagnosed a complete response to S-1 and CDDP in early-stage esophageal cancer. Due to grade 3 diarrhea in the first course, a second course of chemotherapy was carried out with an 80% dose reduction, followed by distal gastrectomy. Over the next 6 months, periodic upper gastrointestinal endoscopy was carried out to detect any further possible esophageal lesions. Currently, the patient remains on an outpatient chemotherapy consisting of S-1 at a dose of 80 mg/m^2 per day for 14 consecutive days followed by a 14-day, drug-free interval. A periodically performed upper gastrointestinal endoscopy, executed in December 2009, revealed no new tumor lesions. The patient was still alive at publication, with no sign of recurrence at 16 months after disappearance of the original tumor.

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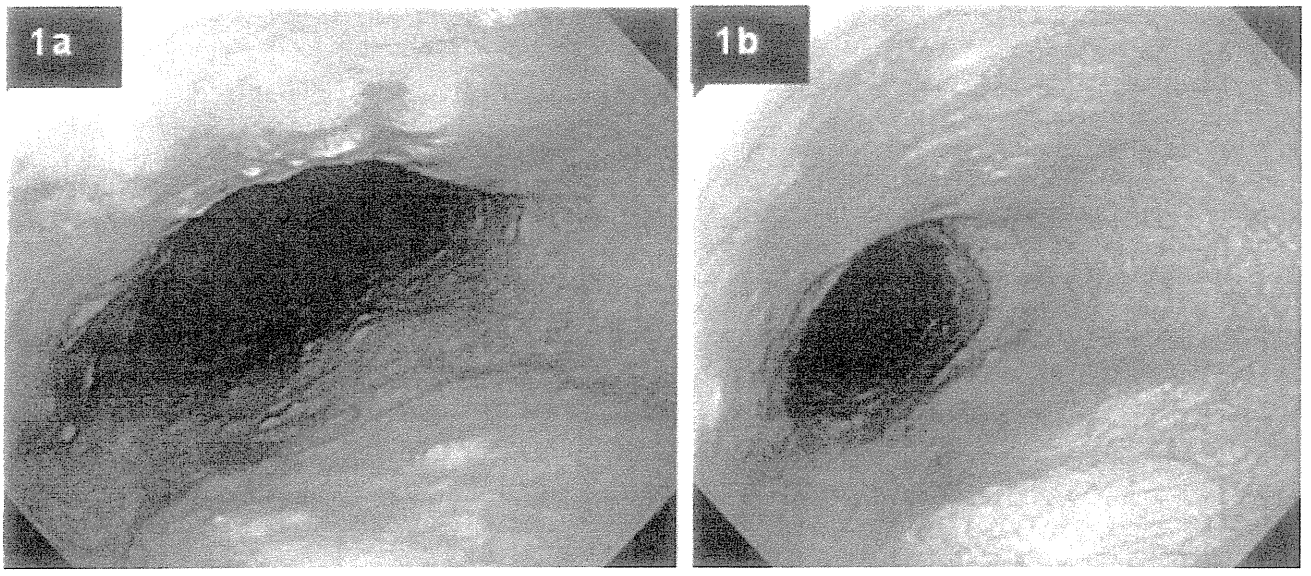

Figure 1. *a. In May 2009, upper gastrointestinal endoscopy disclosed mid-esophageal type IIc tumor measuring 2.0 cm × 1.5 cm. b. In August 2009, after first course of S-1 plus CDDP, upper gastrointestinal endoscopy revealed complete disappearance of tumor, and no further lesions were identified.*

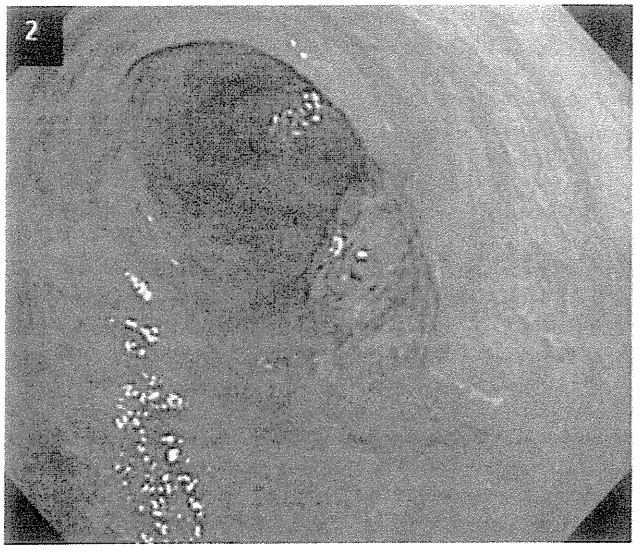

Figure 2. *In May 2009, upper gastrointestinal endoscopy disclosed Bormann type II tumor in stomach measuring 3.5 cm × 3.5 cm.*

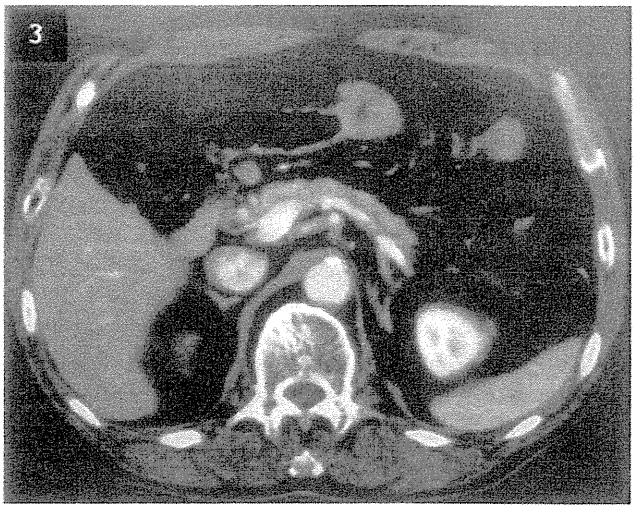

Figure 3. *Computed tomography revealed multiple lymph node metastases around stomach.*

Discussion

Reports of a complete response to chemotherapy in early-stage esophageal cancer are very rare. Several prospective trials have reported that complete response to chemotherapy in advanced esophageal cancer is 2.0-5.6% (5-9). However, this extremely low complete response rate may be due to the fact that the standard treatment in such cases is surgical or endoscopic mucosal resection.

Our results suggest that chemotherapy may be effective against early-stage esophageal cancer. Recently, the effect of docetaxel and CDDP plus 5-fluorouracil (DCF) in gastroesophageal cancer was reported. The overall survival time was 9.2 months. However, grade 3 or 4 treatment-related adverse events occurred in 69% of patients on DCF (5, 6). This suggests that DCF may be unsuitable for early-stage esophageal cancer due to the high rate of adverse side effects.

Chemotherapeutic regimens, including S-1, have recently produced clinical responses and survival benefits in patients with gastric cancer in Japan; even in non-resectable, advanced gastric adenocarcinoma and head and neck squamous cell carcinoma (10, 11). The efficacy of S-1 has also been demonstrated in the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) (12). S-1 has many advantages. These include a high efficacy, excellent tolerability, a good side effect profile, and suitability for administration in an outpatient setting. Furthermore, the combination of S-1 and CDDP has been shown to be efficacious for stage IV gastric adenocarcinoma and head and neck squamous cell carcinoma (13, 14), as well as in neoadjuvant chemotherapy for unresectable advanced gastric cancer (15, 16).

The patient was emotionally upset at the time of diagnosis of early-stage esophageal and advanced gastric cancer, which occurred during his follow-up examination. We hypothesized that administration of neoadjuvant chemotherapy for concurrent advanced gastric cancer provided the unique opportunity for a complete response to take place in his early-stage esophageal cancer.

Either chemotherapy or surgical resection, with or without esophageal preservation is usually selected as the initial treatment for advanced esophageal cancer. However, in terms of dysphagia, the functional outcome of esophagectomy is worse than that of chemotherapy (17). Furthermore, esophagectomy is associated with high mortality and morbidity rates. Surgical mortality rates have been reported as high as 5%, even at high-volume centres (18). This suggests that chemotherapy may offer functional and prognostic merits over esophagectomy in patients with early-stage esophageal cancer.

In conclusion, this case confirms the potential for complete response to S-1 plus CDDP chemotherapy in early-stage esophageal cancer. The accumulation of further such cases may enhance our understanding of this phenomenon and lead to the development of new treatment strategies for early-stage esophageal cancer.

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Complete Response to Chemoradiotherapy in a Patient with Synchronous Double Gastric and Esophageal Cancer

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Abstract. *A 77-year-old man with early synchronous double primary gastric and esophageal cancer showed complete response (CR) to chemoradiotherapy (CRT) with fluorouracil (5-FU) and cis-diamminedichloroplatinum (CDDP) and 60 Gy total dose of radiation. Gastrointestinal endoscopy had revealed type IIc squamous cell carcinoma in the lower oesophagus and type IIc adenocarcinoma in the mid-stomach region. Synchronous double primary early-stage esophageal and gastric cancer was diagnosed. The patient's age and chronic obstructive pulmonary disease (COPD) contraindicated radical esophageal surgery. Therefore, we decided to first administer CRT with 5-FU and CDDP for the esophageal cancer, and subsequently perform partial gastrectomy for the gastric cancer. After the CRT, neither of the tumors recurred. CR to CRT for the esophageal cancer and CR to chemotherapy for the gastric cancer were achieved. Conclusion: CRT with 5-FU and CDDP can produce CR in cases of early esophageal and gastric cancer.*

The standard treatment for early stage esophageal and gastric cancers is esophagectomy and gastrectomy without endoscopic mucosal resection, respectively. Although the prognosis of early-stage gastric cancer has improved owing to the advances in endoscopic therapy, the prognosis of early-stage esophageal cancer remains relatively poor (1, 2). The prognosis of double primary cancer in patients with esophageal cancer is worse than that of a single malignancy (3). Furthermore, synchronous double primary gastric cancer has a worse prognosis than metachronous cancer (4-6). Cases of complete response (CR) to chemoradiotherapy (CRT) administered for synchronous double primary early-stage esophageal and gastric cancer are rare. Here, we report one such case.

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Key Words: Double gastric and esophageal cancer, chemoradiotherapy, complete response.

Case Report

A 77-year-old man who had undergone surgery for prostrate carcinoma was consulting his family doctor for postoperative follow-up and chronic obstructive pulmonary disease (COPD). In July 2007, he was referred to the Department of Digestive Surgery, Nihon University School of Medicine, Itabashi Hospital, because of esophageal and gastric tumors that were identified during a follow-up examination. Upper gastrointestinal endoscopy revealed two 2.5×2.5 cm, type IIc tumors: one in the lower esophagus (Figure 1A) and the other in the lower stomach (Figure 2A). Analysis of the biopsy specimens revealed that that the esophageal tumor was a moderately differentiated squamous cell carcinoma, while the gastric tumor was a moderately differentiated adenocarcinoma. The patient's condition was diagnosed as early stage synchronous double primary cancer of the esophagus and stomach. Computed tomography did not show any evidence of metastasis.

The patient's age and COPD contraindicated radical esophageal surgery. Therefore, we decided to first administer CRT with fluorouracil (5-FU) and *cis*-diamminedichloroplatinum (CDDP) for the esophageal cancer, and subsequently perform partial gastrectomy for the gastric cancer. CRT was carried out according to the Japan Clinical Oncology Group (JCOG) 9516 regimen (7). CDDP was administered at a dose of 100 mg/m^2 on days 1 and 29, and 5-FU was administered at a dose of 900 mg/m^2 daily from days 1 to 4 and 29 to 32. Fractionated radiotherapy was administered from days 1 to 21 and 29 to 49; a total dose of 60 Gy was administered 5 times a week at the rate of 2 Gy fraction. The radiation fields encompassed the primary esophageal lesion and regional lymph nodes. After the completion of the CRT, the response of the tumor to the CRT was clinically and pathologically evaluated by performing upper gastrointestinal endoscopy: the esophageal and

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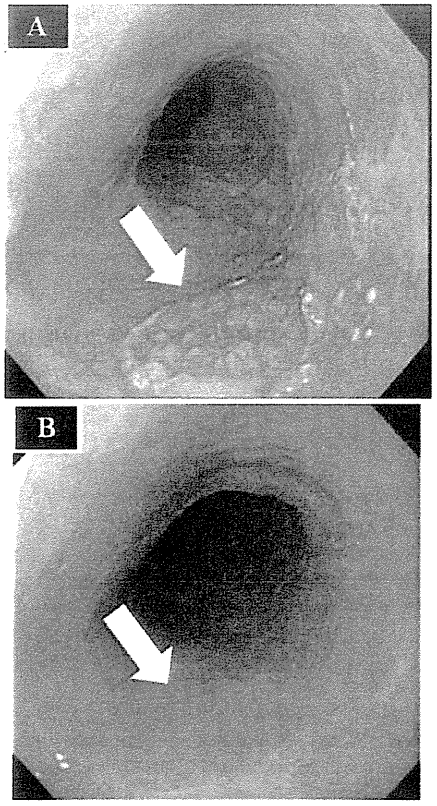

Figure 1. *A: In July 2007, upper gastrointestinal endoscopy revealed a 2.5×2.5 cm, type IIc, mid-esophageal tumor. B: In September 2009, after the chemoradiotherapy, upper gastrointestinal endoscopy revealed complete disappearance of the mid-esophageal tumor and absence of new lesions.*

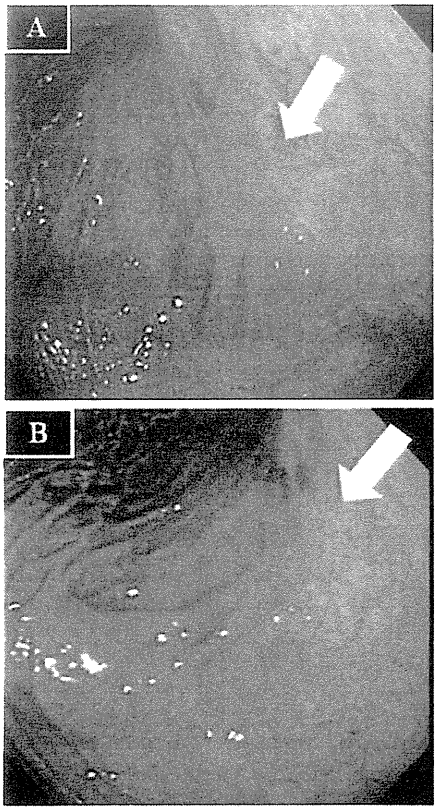

Figure 2. *A: In July 2007, upper gastrointestinal endoscopy revealed a 2.5×2.5 cm, type IIc, tumor of the lower stomach. B: In September 2009, after the chemoradiotherapy, upper gastrointestinal endoscopy revealed complete disappearance of the tumor of the lower stomach and absence of new lesions.*

gastric tumors were found to have regressed to scar lesions (Figure 1B) and (Figure 2B). The biopsy specimens obtained from both the scar lesions were negative for cancer. We concluded that the patient showed CR to CRT for the early esophageal cancer and CR to chemotherapy for the gastric cancer. Over the next 4 months, periodic upper gastrointestinal endoscopic examinations were conducted to detect any further esophageal or gastric lesions. After CRT, the patient did not receive adjuvant chemotherapy or any other anticancer treatment. By August 2010, upper gastrointestinal endoscopy had been performed thrice, and no further lesions had been identified. At 33 months after the complete disappearance of the tumors, the patient is still alive without any signs of tumor recurrence.

Discussion

Cases of CR to CRT administered for synchronous double primary early-stage esophageal and gastric cancer are rare. Several retrospective studies have reported a CR rate of 17-36% to CRT for advanced esophageal cancer (8-10). However, the efficacy of CRT in the treatment of early esophageal cancer is still unknown. In contrast, the rate of the CR to chemotherapy for advanced gastric cancer is as low as 0-0.7% (11, 12). CR to chemotherapy for early gastric cancer is very rarely reported because most cases are treated with surgical resection or endoscopic mucosal resection as these procedures give good clinical results. Moreover, dysphagia after gastrectomy is not as severe as that after esophagectomy, and gastrectomy is not highly associated with high mortality and morbidity.

CRT may be effective in early oesophageal cancer (13), and chemotherapy in early gastric cancer. Although advances in endoscopic therapy have improved the prognosis of early esophageal cancer (14, 15), the outcome is still not acceptable (1, 2). Cases of CR to CRT administered for synchronous double primary early stage esophageal and gastric cancer are rare. In general, either radiotherapy or surgery with or without esophageal preservation is selected

as the initial treatment. Only a few studies have reported the efficacy of CRT for early-stage esophageal cancer, and the optimal treatment approach is still undefined. The dysphagia experienced after esophagectomy is worse than that experienced after CRT (16). Furthermore, esophagectomy is associated with high mortality and morbidity, being associated with a 5% surgical mortality rate even at high-volume centers (12). Some studies have compared the outcomes of esophagectomy with those of CRT in a population-based sample of elderly patients with early-stage esophageal cancer; the survival rate of patients with squamous cell carcinoma did not significantly differ between CRT and esophagectomy groups. Patients with radio- and chemosensitive early esophageal cancer seem to have prognostic and functional merit (17).

In our patient, we hypothesize that CRT administration for the concurrent early stage esophageal cancer stimulated the response of the gastric cancer to chemotherapy. Chemosensitivity to 5-FU and CDDP is not very suitable for advanced gastric cancer (18). In Japan, S-1 (Taiho Pharmaceutical, Tokyo, Japan) is a key chemotherapeutic agent used against gastric cancer (19). Its efficacy has been proven in trials of S-1 for gastric cancer and the combination of S-1 and CDDP for stage IV gastric cancer patients (12). S-1 has many advantages, including its high efficacy, excellent tolerability, low side-effect profile, and the ease of administration in an outpatient setting. In the light of our case, we believe that patients with early gastric cancer could be cured by using highly efficacious S-1 chemotherapy. Further research is needed to improve esophageal and gastric preservation in patients with early cancer.

In conclusion, this case confirms the possibility of CR to radiotherapy and chemotherapy for early esophageal and gastric tumors. Further study of such cases will promote further understanding of CR, and it may also lead to the development of a new treatment strategy for early esophageal and gastric cancer.

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症 例

S-1単独療法が著効し組織学的CRが得られた高度進行残胃癌の1例

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A Patient with Advanced Remnant Gastric Cancer Responding Completely to S-1 Monotherapy: Asuo Okaniwa[*1], Isao Murayama[*1], Yoshihiro Watanabe[*1], Ichiro Hayashi[*1], Tetsuo Hasegawa[*1], Yuichi Kasakura[*2], Noriko Kinukawa[*3], Norimichi Nemoto[*3] and Masashi Fujii[*4] ([*1]*Dept. of Surgery, Sonoda Dai-ichi Hospital*, [*2]*Dept. of Surgery, Sonoda Dai-san Hospital*, [*3]*Dept. of Pathology, Surugadai Nihon University Hospital*, and [*4]*Dept. of Digestive Surgery, Nihon University School of Medicine*)

Summary

A 74-year-old man with anemia visited our hospital. When he was 42 years old, he was diagnosed with duodenal ulcer and underwent gastrectomy with Billroth Ⅱ construction. A gastrointestinal endoscopic examination revealed an ulcerative lesion at the remnant stomach, and the pathological examination of the biopsy specimen showed moderate to poorly differentiated adenocarcinoma. Abdominal CT scan revealed liver and para-aortic lymphnode metastases. He received daily oral administration of S-1 at a dose of 100 mg/body, bid, 4 weeks on and 2 weeks off. After 4 courses of S-1, CT scan showed a complete response of the liver and also para-aortic lymphnode metastasis. He underwent total remnant gastrectomy with D2 dissection. Histological examination revealed no residual cancer cells in the surgically removed stomach and lymphnodes, and he was diagnosed a complete pathological response (Grade 3). He refused adjuvant S-1, but is in good health without recurrence 2 years after the operation. Key words: S-1, Pathological CR, Remnant gastric cancer (*Received Apr. 15, 2011/Accepted May 11, 2011*)

要旨 われわれは初診時切除不能残胃癌に化学療法が奏効し，根治切除施行，病理学的CRが得られた症例を経験したので報告する。症例は74歳，男性。42歳時，十二指腸潰瘍にて幽門側胃切除Billroth Ⅱ法再建が施行されている。貧血を指摘され，当科を受診した。精査の結果，残胃癌，肝転移，大動脈周囲リンパ節転移にて根治切除不能と診断し，S-1単剤で4週投与2週休薬にて治療を開始した。3コース終了後CT上肝転移，大動脈周囲リンパ節が消失，さらに1コース投与後CRと判定した。患者の承諾を得て審査開腹し，根治切除可能と判断し残胃切除術を施行した。切除標本にて病理組織学的CRと診断された。補助化学療法は患者拒否により施行していないが，術後2年現在再発なく生存中である。

はじめに

最近の化学療法の進歩により根治切除不能胃癌に化学療法が奏効し，根治切除可能となる症例を頻繁に経験するようになった。また，それらの症例のなかには病理学的complete response（CR）がみられたとする報告もある[1-6]。残胃癌は診断が困難であり，初診時に根治切除不能症例も多い。われわれは残胃癌，肝転移，大動脈周囲リンパ節転移にて根治切除不能と診断し，S-1単剤にて治療を開始，CT上肝転移，大動脈周囲リンパ節が消失したため審査開腹し，根治切除可能と診断して手術を施行，切除標本にて病理組織学的CRと診断された症例を経験したので報告する。

Ⅰ．症 例

患者: 74歳，男性。

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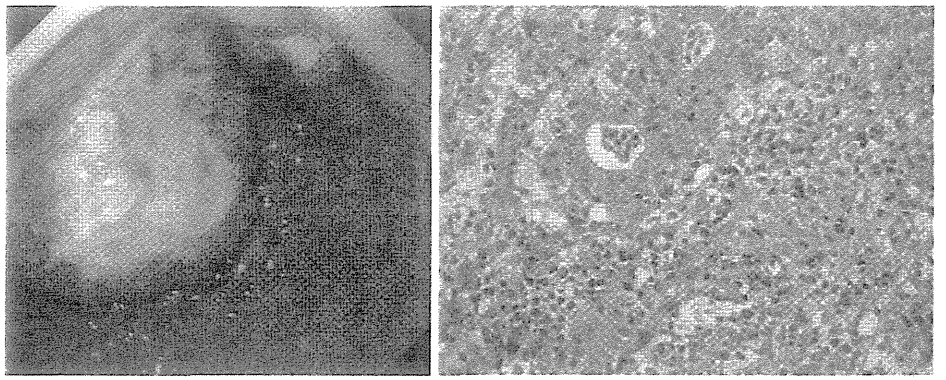

図 1 化学療法前内視鏡，病理所見
a: 噴門より 5 cm の前弯～小弯にかけて半周性の 2 型腫瘍を認めた。
b: 生検による病理組織診断は中分化～低分化型腺癌であった。

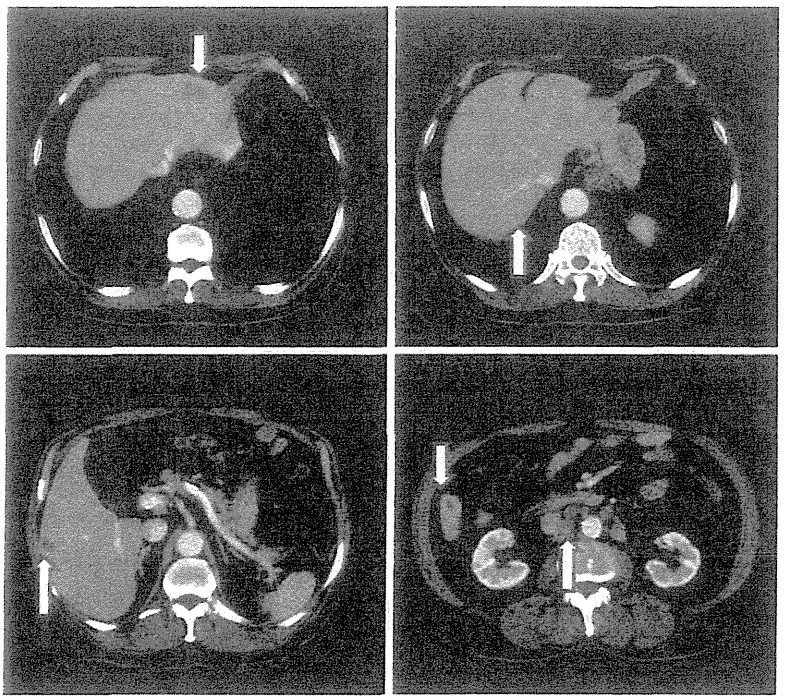

図 2 化学療法前腹部 CT
残胃全体の壁肥厚あり。肝 S3，S5，S6 に多発の肝転移を認め，残胃小弯ならびに大動脈周囲（No. 16）に多数のリンパ節の腫大を認めた。

主訴: 貧血。

既往歴: 42 歳時 十二指腸潰瘍。他院にて幽門側胃切除 Billroth Ⅱ法再建，66 歳時 視床出血。

家族歴: 特記すべきことなし。

現病歴: 視床出血治療後，当院脳神経外科外来通院中であった。定期検査にて貧血を指摘され，精査目的で当科を受診した。

初診時現症: 身長 167 cm，体重 79 kg。体温 36.0℃。眼瞼結膜にやや貧血を認め，眼球結膜に横染なし。腹部は平坦・軟で，腫瘤・表在リンパ節は触知しない。腹部正中に手術瘢痕を認めた。

初診時検査所見: Hb 8.2 g/dL と貧血を認める以外特記する異常値はみられなかった。CEA 2.1 ng/mL，CA19-9 1.2 U/mL，AFP 3.8 ng/mL で，腫瘍マーカーはそれぞれ正常値範囲内であった。上部消化管造影では残胃吻合部の狭窄が認められ，上部消化管内視鏡検査にて噴門より 5 cm から前弯～小弯にかけて半周性の 2 型腫瘍を認めた（図 1a）。生検による病理組織診断は中分化～低分化型腺癌であった（図 1b）。腹部 CT 検査にて残胃全体の壁肥厚あり。肝 S3，S5，S6 に多発の肝転移を認め，残胃小弯ならびに大動脈周囲（No. 16）に多数のリンパ節の腫大を認めた（図 2）。

治療経過: CT による評価から胃癌取扱い規約（旧 13 版）に基づき cTX，cN3，cM0，cH1，cP0: c-Stage Ⅳと診断し，患者の同意を得て S-1 による化学療法を開始した。S-1 100 mg/day を初回は 2 週間投与 1 週間休薬と

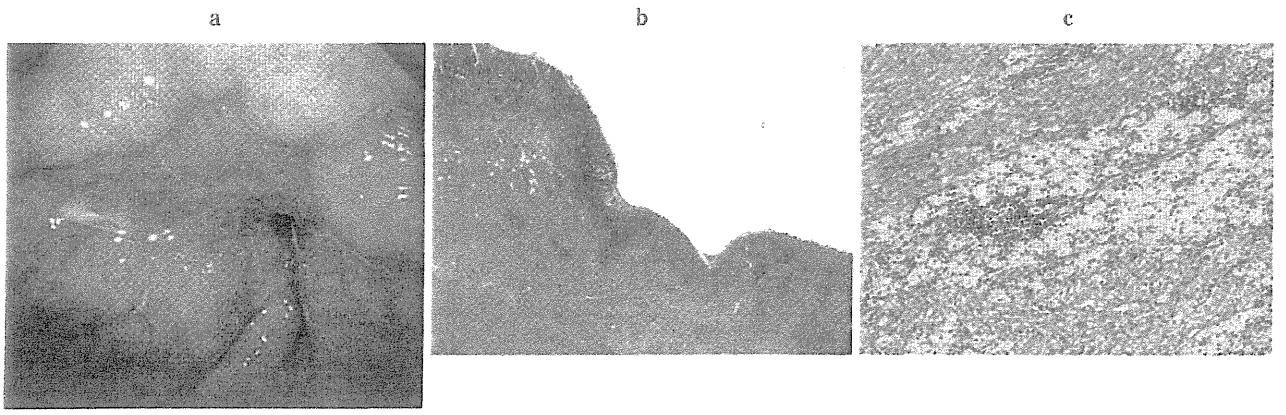

図 3　術後内視鏡，病理所見
a: 化学療法後の上部消化管内視鏡では，腫瘍はⅡc様に変化し生検ではGroup Ⅱの所見であった。
b: 組織標本は壊死組織を伴う潰瘍であり，固有筋層～漿膜下に及ぶ線維化がみられた。
c: マクロファージとリンパ球の集族が筋層内に認められるがviableな腫瘍組織は認められない。

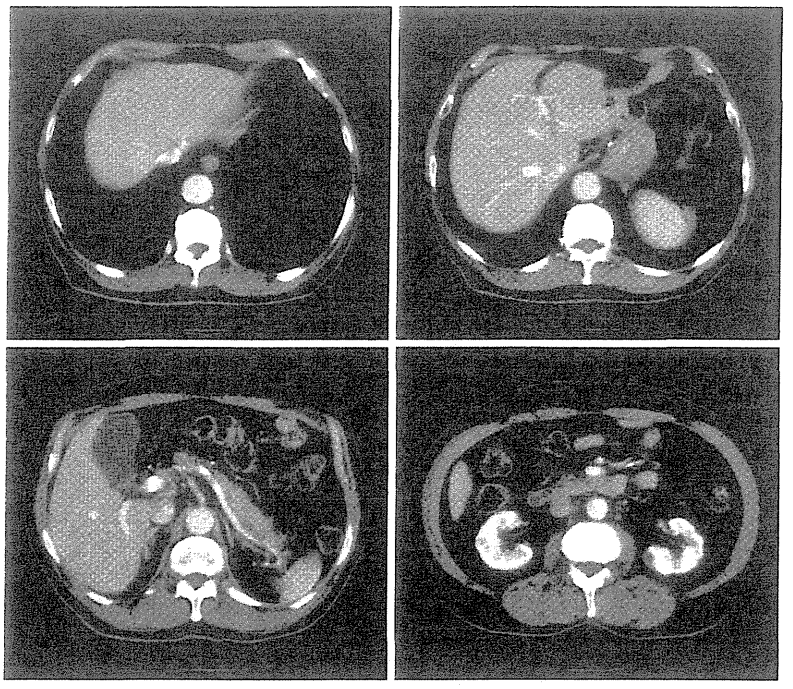

図 4　化学療法後腹部CT
残胃の壁肥厚はほぼ消失。多発の肝転移もほぼ消失，さらに大動脈周囲を含めたリンパ節腫脹も消失した。

し，有害事象のないことを確認後，以後4週投与2週休薬とした。3コース施行後の内視鏡検査にて，腫瘍はⅡc様に変化し（図3a），生検にてGroup Ⅱ，CT検査で胃の壁肥厚はほぼ消失。多発肝転移もほぼ消失，さらにリンパ節腫脹も消失した。そのため原発巣・転移病巣ともにCRと判断した（図4）。

その後も4週投与2週休薬を1コース続けた後のCT診断により，引き続きCR継続のため患者の同意を得て，化学療法開始から6か月後に試験開腹術を施行した。

試験開腹による術中所見では，少量の腹水を認め，細胞診に提出した。残胃は結腸前Billroth Ⅱ法再建がなされているがBraun吻合はない。肉眼的肝転移消失，大動脈周囲リンパ節腫脹なし，腹膜播種なく根治切除可能と判断，あらかじめ患者の承諾を得ており，残胃全摘術（D2リンパ節郭清）にコンバートし，Roux-en Y吻合再建を行った。

切除標本肉眼所見: 残胃（U領域）吻合部近傍に瘢痕化を伴う陥凹性病変が認められた。

病理組織学的所見: 腹水細胞診陰性。摘出残胃病変は潰瘍底壊死組織を伴う潰瘍であり，固有筋層～漿膜下に及ぶ線維化がみられた。マクロファージとリンパ球の集族は認められたがviableな腫瘍組織は認められず，リンパ節転移（0/7）病理学的CRと診断された（図3b，c）。患者は，術後合併症なく第21病日に軽快退院した。術後

補助化学療法は患者の同意を得られず施行していない。現在，術後2年経過し再発兆候はみられず社会生活を営んでいる。

Ⅱ．考　察

残胃癌は初回胃切除から10年以上経過してから発症しやすいといわれ，胃外科術後障害研究会の全国アンケート調査[7]の887例では再建別法でBillroth Ⅰ法が368例，Billroth Ⅱ法が519例集計された。このうち初回良性は65.2%（578/887）である。残胃癌手術までの介在時間はBillroth Ⅰ法が21.1年，Billroth Ⅱ法が31.5年と報告されている。組織型は分化型，未分化型はほぼ同数である。残胃占拠部位はBillroth Ⅰ法では非断端部，Billroth Ⅱ法では吻合部に多いと報告されている。本症例はBillroth Ⅱ法再建術後32年であり，病変の主体は吻合部近傍，組織型は中～低分化腺癌であった。

切除不能残胃癌の治療は通常の切除不能胃癌と同様化学療法が第一選択となる。しかしながら，初回手術による血管構築破壊による薬剤到達性や，経口剤の吸収や薬理動態などの報告はほとんどない。また，残胃癌が化学療法に奏効しconversion treatmentに移行できた症例の報告も少なく，組織学的CR例も極めてまれである[8]。

進行再発胃癌の標準的化学療法は，JCOG9912の結果，S-1単剤の5-fluorouracil注射剤との非劣性が報告され[9]，続くSPIRITS試験でS-1単剤に比べS-1/cisplatinの優越性が報告された[10]。その結果，S-1/cisplatinが現在標準化学療法として確立されている。しかしながらcisplatinは腎毒性が強く，毒性軽減のために大量の補液を必要とするため入院治療が余儀なくされる。外来通院での実施可能性を求めて，TOP-002試験ではS-1単剤とS-1/CPT-11との比較試験[11]，JACCRO GC-03試験（START trial）ではS-1単剤とS-1/docetaxelとの比較試験[12]が行われている。しかしながら，両試験とも統計学的な優越性が得られず，現在もS-1/cisplatinのみが標準化学療法としてガイドライン治療として推奨されている。

本症例でも標準化学療法であるS-1/cisplatin併用療法の説明を行ったが，患者の希望により入院治療を要しないS-1単独療法を選択した。また，残胃症例のため消化器系有害事象の発現を考え推奨用量である120 mg/body（80 mg/m^2）から100 mg/bodyに減量して治療を開始し，有害事象を観察後に推奨用量への漸増を考えていた。しかしながら，100 mg/bodyにても効果発現がみられたため，以後も100 mg/bodyで治療を継続した。

S-1単剤の臨床効果におけるCR例については，第Ⅱ相試験で1例(1/101)みられている[13]。その後，SPIRITS試験ではS-1単剤群で1例（1/106），S-1/cisplatin併用群で1例（1/87）のCR例がみられ，TOP-002試験ではS-1単剤群（0/93），S-1/CPT-11群（0/94）両群ともCR例はみられず，JACCRO GC-03試験において，S-1単剤群で4例（4/244），S-1/docetaxel併用群で1例（1/228）のCR例が報告されている。上記3試験におけるS-1単剤におけるCR率は1.13%（5/443），併用群におけるCR率は0.49%（2/409）であり，CR例はむしろ単剤群に多くみられている。

SPIRITS試験ならびにJACCRO GC-03試験における層別解析では，腹膜播種などの標的病変のない症例ではS-1/CDDP，S-1/docetaxelなどの併用群で有意に生存期間の中央値の延長が証明されたが，肝転移やリンパ節転移などの標的病変のある症例では，S-1単剤と併用群の生存期間の中央値に差がないとの報告がある。本症例のような残胃原発巣，肝転移，リンパ節転移を有するような標的病変のある症例には，患者の状態，希望によりS-1単剤での治療開始も念頭に入れてもよいと考えられる。

本症例は化学療法が奏効し，根治切除可能になったために結果的に術前に化学療法が行われたことになる。しかしながら，術前化学療法には二通りのコンセプトがある。一つは真の意味での術前化学療法であり，術前臨床診断にて拡大リンパ節郭清や合併切除により根治切除可能ではあるが，非根治切除も予想される症例を対象として，ダウンステージングを期待して行うneoadjuvant chemotherapy（NAC）である。もう一つは術前診断根治切除不能例を対象として行った化学療法が奏効し，結果的に臨床上根治切除可能となった本症例のような場合で，pseudo NACあるいはconversion treatmentと称される。本症例は典型的なconversion treatmentである。

術前化学療法はヒトによる制癌剤感受性試験と考えられる。本症例でS-1単独療法が効果を発揮した要因としては，腫瘍のS-1に対する高感受性が考えられる。われわれは，切除可能大腸癌において術前2週間の短期UFT投与後に切除標本の組織学的効果を検討した。その成績でもGrade 3の効果がみられた症例が126例中3例，Grade 2以上の効果は25%にみられている[14]。本症例は，S-1単剤にて期待できる約1%の臨床的CR症例がconversion treatmentにより組織学的に証明された残胃癌では極めてまれな症例と考えている。患者は術後補助化学療法を希望せず経過観察中であるが，再発時には高感受性を示したS-1をベースにした化学療法での再治療を考えている。

おわりに

S-1単独療法で組織学的CRが得られた肝転移を有する切除不能残胃癌の1例を報告した。S-1/cisplatin療法が進行再発胃癌の標準化学療法であるが，計測可能病変である肝転移，リンパ節転移症例においてはS-1単剤治療にても奏効し，conversion treatmentへの移行や生命延長効果が期待される。

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