didates for those phase II trials. Moreover, the long-term outcomes of patients after S-1 monotherapy for metastatic gastric cancer are unclear. The aim of this retrospective study was to investigate, using multivariate analysis, the outcomes and characteristics of long-term survivors of metastatic gastric cancer who had initially received S-1 monotherapy.

Patients and methods

A total of 92 patients with advanced gastric cancer who had received S-1 as first-line chemotherapy between April 1999 and March 2001 at the National Cancer Center Hospital East, Kashiwa, Japan, were analyzed retrospectively. S-1 was administered orally at 80 mg/m^2 per day for 4 weeks, followed by a 2-week rest, and then repeated every 6 weeks until disease progression, unacceptable toxicity, or patient refusal. We clinically diagnosed peritoneal dissemination by imaging techniques such as computed tomography (CT) or barium enema. If an abdominal CT scan showed massive ascites or barium enema revealed multiple areas of tethered fold-type stenoses, with normal segments, and frequent localization in the transverse colon,[12] we recognized peritoneal dissemination. In addition, we diagnosed peritoneal metastases if a laparotomy or laparoscopy was performed and peritoneal dissemination was identified histologically. The responses of metastatic lesions were assessed according to the World Health Organization criteria. Toxicity was graded according to the National Cancer Institute Common Criteria during all of the treatment courses.

Statistical analysis

Overall survival was defined as the period from the date of the first course of chemotherapy to the date of death from any cause. Progression-free survival was defined as the period from the date of the first course of chemotherapy to the date of disease progression or death, whichever occurred first. If neither event had occurred at the time of the last record, the patient was censored at that time. Survival and progression-free survival were calculated by the Kaplan-Meier method, and the significance of differences between survival curves was determined by the log rank test. Multivariate analysis of prognostic factors was performed by the Cox proportional hazard method, using as variables sex (male, female), age (<60 or ≥60 years), performance status (PS) (0, 1, or 2–3), history of gastrectomy (+, –), macroscopic type (scirrhous, nonscirrhous), histological type (intestinal, diffuse), number of metastatic sites (1, ≥2), and second-line chemotherapy (+, –).

Results

Patient characteristics

The baseline characteristics of the 92 patients are listed in Table 1. Eighty-six patients (93%) had a good performance status of 0 to 1, and 70 (76%) had measurable metastatic lesions. Thirty-seven patients (40%) had undergone gastrectomy before first-line chemotherapy. Major sites of metastases were lymph nodes in 55 patients (60%), peritoneum in 48 (52%), and liver in 27 (29%). All of the patients were treated on an outpatient basis during most of the treatment period. Among the 89 patients who became refractory to S-1 treatment alone, 57 (64%) received second-line chemotherapy regimens. The most frequently used second-line treatment regimens were cisplatin plus irinotecan (17/57), methotrexate plus 5-FU (14/57), irinotecan plus mitomycin C (11/57), and docetaxel monotherapy (10/57).

Toxicity

All of the treated patients were assessed for toxicity. A total of 433 cycles were administered, with a median of 3.5 cycles per patient (range, 1–19). The maximum toxicity grades observed for each patient are listed in

Table 1. Patient characteristics

Characteristic	No. of patients (n = 92)
Sex	
Male	56
Female	36
Age (years)	
Median (range)	59 (28–78)
ECOG performance status	
0	62
1	24
2	5
3	1
Macroscopic type of primary tumor	
Scirrhous type	27
Nonscirrhous type	65
Histological type	
Intestinal type	34
Diffuse type	58
History of gastrectomy	
+	37
–	55
Metastatic sites	
Lymph node	55
Peritoneum	48
Liver	27
Others	10
Number of metastatic sites	
1	48
≥2	44

ECOG, Eastern Cooperative Oncology Group

Table 2. The incidence rate of grade 3 or 4 toxicity was less than 10%, except for grade 3 or 4 anemia in 11 patients (12%). Eight (9%) patients died within 30 days of the last administration. However, these patients died of tumor progression, and no treatment-related deaths were observed.

Response and survival

The overall response rates are listed in Table 3. Of the 70 patients assessable for tumor response, we observed two (2.9%) complete responses and 23 (32.9%) partial responses, giving a response rate of 35.7% [95% confidence interval (CI), 24.5%–46.9%]. As to efficacy by site, the response rate was 26% (7/27) for liver metastases and 38% (21/55) for lymph node metastases. With a median follow-up of 3.1 years, the median progression-free survival time was 4.6 months. The median survival time was 11.9 months with 1-, 2-, and 3-year survival rates of 49.1%, 22.8%, and 9.8%, respectively (Fig. 1).

Of particular note was that among 48 patients with a single metastatic site, 22 in whom the metastasis was limited to the peritoneum alone had longer survival times (median survival, 24 months) than patients with single metastases at other sites (median survival, 12.6 months) ($P = 0.062$; Fig. 2). On the other hand, median survival of 15 patients with lymph node metastasis alone was 12 months, which is not long compared with the survival of patients with peritoneal dissemination alone. Only six patients had liver metastasis alone.

Table 2. Toxicity profiles

Toxicity	Grade (NCI-CTC) 1	2	3	4	Grade 3/4 (%)
Hematological toxicity					
Leukopenia	28	17	2	1	3
Neutropenia	28	7	3	1	4
Anemia	30	37	5	6	12
Thrombocytopenia	12	3	3	0	3
Nonhematological toxicity					
Nausea	19	8	0	0	0
Diarrhea	16	9	2	0	2
Anorexia	31	11	1	0	1
Stomatitis	13	2	0	0	0
Skin rash	14	3	0	0	0
AST	37	3	2	0	2
ALT	23	5	1	0	1
Bilirubin	20	20	2	0	2
Creatinine	4	1	1	0	1

NCI-CTC, National Cancer Institute Common Toxicity Criteria; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 3. Tumor response ($n = 70$)

Response	No. of Patients	%
Complete response	2	3
Partial response	23	33
Stable disease	27	38
Progressive disease	18	26

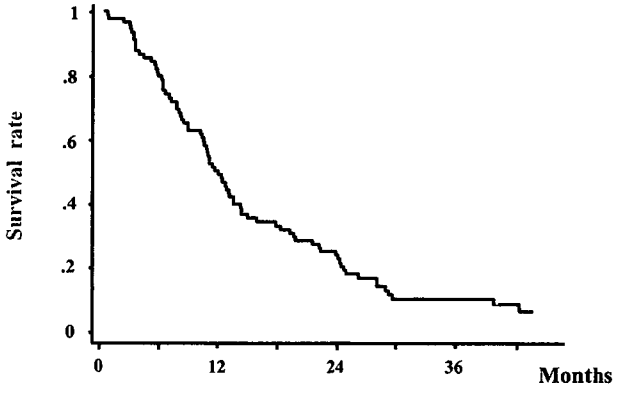

Fig. 1. Overall survival curve for all patients. The median survival time was 11.9 months with 1-, 2-, and 3-year survival rates of 49.1%, 22.8%, and 9.8%, respectively

Table 4. Characteristics of 3-year survivors

Age (years)	Sex	PS	Macroscopic type	H	MS	Surgical resection	Response	Treatment cycle	Survival (months)	Present status
63	M	1	N	D	A-LN	+	PR	12	37	A
65	M	0	N	I	P	+	NE	6	40	D
61	M	1	N	D	P/A-LN	–	PR	12	43	A
44	F	0	S	D	P	+	NE	6	43	D
33	M	0	N	D	P	+	NE	15	44	A
28	F	0	S	D	P	–	NE	7	45	D
70	M	0	N	I	P	+	NE	13	49	A
78	M	0	N	I	A-LN	–	CR	12	62	A
56	F	0	S	D	P	+	NE	6	62	A

M, male; F, female; PS, performance status; N, nonscirrhous; H, histology; I, intestinal; D, diffuse; MS, metastatic site; A-LN, abdominal lymph node; P, peritoneum; CR, complete response; PR, partial response; NE, not evaluable; A, alive; D, dead

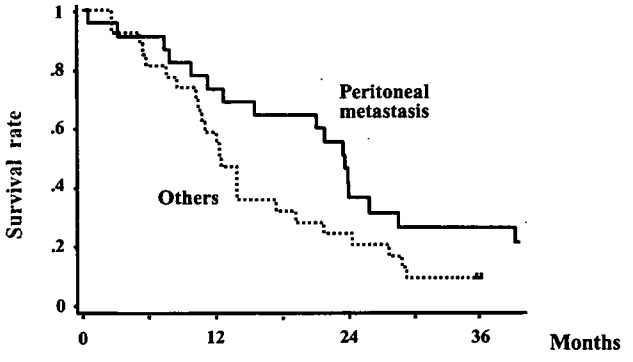

Fig. 2. Survival curves for 22 patients with peritoneal metastasis (*solid line*, median survival, 24 months) and 26 patients with metastases at other single sites (*dotted line*, median survival, 12.6 months)

Characteristics of the nine 3-year survivors are summarized in Table 4. All of these nine patients had good PS grades of 0 or 1. The metastatic sites in these patients included the peritoneum alone in six, abdominal lymph nodes alone in two, and peritoneum and abdominal lymph nodes in one. These patients received a median of 12 treatment cycles (range, 6–15). Three patients were alive with no apparent tumor progression at 3 years after S-1 monotherapy; one of them originally had abdominal lymph node metastases alone, and the others had peritoneal metastases alone. The other six patients received second-line treatment such as methotrexate plus 5-FU or docetaxel monotherapy. Six patients had undergone surgical resection before the start of S-1 monotherapy, and the remaining three did not undergo surgical resection during the follow-up period.

Multivariate analysis

Multivariate analysis of baseline characteristics was conducted to investigate their utility for predicting survival. Good PS and only one metastatic site were found to be significant independent prognostic factors (Table 5).

Table 5. Prognostic factors in the multivariate analysis

Variables	HR	95% CI	*P* value
Sex			
Male	1		
Female	1.37	0.77–2.43	0.28
Age (years)			
<60	1		
≥60	1.16	0.71–1.91	0.56
ECOG PS			
0–1	1		
2–3	8.33	2.62–26.5	0.0003
Macroscopic type			
Scirrhous type	1		
Nonscirrhous type	1.18	0.66–2.11	0.57
Histological type			
Diffuse type	1		
Intestinal type	1.39	0.80–2.39	0.24
History of gastrectomy			
+	1		
–	1.19	0.74–1.93	0.5
Number of metastatic sites			
1	1		
≥2	2.12	1.26–3.57	0.0048
Second-line chemotherapy			
+	1		
–	1.28	0.77–2.13	0.35

HR, hazard ratio; 95% CI, 95% confidence interval

Discussion

In a previous Japanese phase III study, 5-FU alone was shown to provide a survival benefit almost equivalent to that of 5-FU plus cisplatin (CF) with less toxicity and an apparently better quality of life.[6] In the next Japanese study, 5-FU alone was considered as the reference arm because the primary end point of that study was overall survival. The progression-free survival and median survival times obtained with 5-FU alone were 1.9 and 7.1 months, respectively.[6] In our present study, the progression-free survival and median survival times of patients receiving S-1 monotherapy were 4.6 and 11.9 months, respectively, which were better than those obtained with 5-FU alone in the Japanese phase III trial. Among the patients we studied, 64% received second-line chemotherapy regimens after failure of S-1 treatment, which is comparable to the figure of 57% for 5-FU alone in the phase III trial.[6] However, during the previous Japanese randomized trial, new cytotoxic agents such as irinotecan and taxanes (paclitaxel and docetaxel) were not available, and these might have prolonged the overall survival of the present population who initially received S-1 monotherapy.

Although the CF regimen has demonstrated no survival advantage over 5-FU alone in some randomized trials,[6,7] this combination regimen is the one most widely used worldwide because of its high response rate and long progression-free survival. The median progression-free survival achieved with the CF regimen was 3.9 months in the Japanese trial[6] and 4.1 months in a randomized study conducted by the European Organization for Research and Treatment of Cancer (EORTC).[5] Recently, a randomized phase III trial comparing TCF with CF has been reported. At the final analysis, TCF was shown to have a survival benefit significantly superior to that of CF (9.2 months vs. 8.6 months, respectively), and also a longer time to disease progression (5.6 months vs. 3.7 months).[8] In terms of progression-free survival, S-1 monotherapy in the present study was

slightly superior to the CF regimen in those three randomized trials. Although progression-free survival after S-1 monotherapy was slightly shorter than that after TCF, S-1 monotherapy was superior to TCF in terms of median survival. Although some selection biases in the present study might have been responsible the apparently favorable survival data, S-1 monotherapy as a first-line treatment may have a survival advantage comparable with combination regimens such as CF and TCF, but with less toxicity.

It was noteworthy that 22 patients with metastatic sites limited to the peritoneum had favorable survival with a median survival 24 months, though the number of such patients was small. The median progression-free survival of these patients after S-1 monotherapy was 9.4 months, which was almost twice as long as that for the patients as a whole. Therefore, this result might have contributed to the long median survival. In addition, 16 of these patients with only peritoneal metastasis were diagnosed at laparotomy or by laparoscopy, whereas the remaining six were diagnosed by clinical imaging techniques such as CT or barium enema before treatment. Thus, a possible alternative explanation for these good survival results was better patient selection and earlier detection of peritoneal dissemination. Recently, S-1 has been reported to have the potential to prolong the survival of patients with peritoneal dissemination.[12–14] An experimental study to assess the effect of S-1 on peritoneal dissemination of gastric cancer has confirmed that a high concentration of 5-FU is maintained in the intraperitoneal tumors after S-1 administration, and that survival time is prolonged without any decrease of oral food intake or body weight.[15] Clinically, Osugi et al.[14] has reported that an S-1-treated group showed longer survival than a control group treated mostly with oral fluoropyrimidines or intravenous FP, with a median survival of 257 versus 118 days, although this study was not a randomized one.

In the present study, nine patients survived for 3 years. All of them had good PS and eight had only one site of metastasis, either the abdominal lymph nodes alone or the peritoneum alone. They received a median of 12 cycles of S-1 treatment, and six of the patients received second-line chemotherapy after S-1 monotherapy failed. Therefore, long-term treatment with S-1 and the second-line treatment may have prolonged their survival. On the other hand, among the other three patients without apparent tumor progression at 3 years, two had peritoneal metastasis alone, which was not detected by clinical imaging before S-1 monotherapy, and one had abdominal lymph node metastasis alone. A previous study demonstrated that ten of eleven 5-year survivors had only one metastatic site, and eight of them had abdominal lymph node metastasis alone.[16] Our present findings suggest that patients with peritoneal metastases alone have as good a chance of long-term survival as patients with abdominal lymph node metastases alone when S-1 monotherapy is used as first-line chemotherapy.

Several studies have investigated prognostic factors in patients with advanced gastric cancer.[16–19] Poor PS,[16,17,19] liver metastases,[18,19] peritoneal metastases,[19] an elevated alkaline phosphatase level,[19] multiple metastatic sites,[16] and a scirrhous-type tumor[16,17] were shown to be associated with poor survival. In our study, patients with good PS and only one site of metastasis showed better survival than the others, similar to the data reported previously by Yoshida.[16]

In conclusion, S-1 is a highly active regimen that is generally well tolerated in patients with metastatic gastric cancer. The survival outcomes are promising, particularly in patients with only peritoneal metastasis. Of course, this analysis was retrospective, and the favorable results obtained with this agent will need to be confirmed by an on-going randomized trial being conducted by the Japan Clinical Oncology Group comparing 5-FU alone with CPT-11 plus cisplatin and with S-1 alone.

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内視鏡手技における私の工夫(大腸)

熊谷一秀[1)]，小林清典[2)]

大腸内視鏡検査は，内視鏡医のたゆまない努力と産学協同での新しい内視鏡および関連機器の開発により飛躍的な進歩をとげた。とくに診断面では，経口腸管洗浄液による腸管前処置法の確立や無透視一人法による大腸内視鏡挿入法の普及，さらに拡大内視鏡などの精密診断法が果たした役割が大きい。治療面では，内視鏡的粘膜切除術により表面型腫瘍の内視鏡治療が容易となり，さらに大型の腫瘍に対しては内視鏡的粘膜下層剝離術(ESD)も試みられている。また内視鏡治療に用いる各種処置具の開発も進み，確実かつ安全に内視鏡治療が行なえる環境が整備されてきている。しかし現在の状況が到達点ではなく，大腸領域に限らず内視鏡医は常に診断および治療を確実かつ安全に行うことができ，被検者への侵襲も少ない内視鏡手技を考案し実用化する責務がある。そうした意図から本ワークショップが企画されたものと考える。9題の発表があったが，前半の4題は大腸内視鏡検査法，後半の5題は大腸腫瘍に内視鏡的摘除を行なう際の手技の工夫についてであった。

大島ら(東京医大)と鵜川ら(鵜川医院)は，大腸内視鏡検査における炭酸ガス送気の有用性について報告した。大島らは大腸内視鏡検査例を炭酸ガス送気群と従来群にわけて検討し，炭酸ガス送気は安全で検査後の腹部膨満感の軽減に有効であることを示した。鵜川らは炭酸ガス送気を行う際に必要となる機器を具体的に示し参考になった。

手塚ら(帝京大)は大腸癌イレウスへの経肛門的イレウス管挿入例に対して炭酸ガスを併用したvirtual colonoscopyを行い，閉塞部より口側腸管の術前スクリーニングに有用であることを示した。侵襲が少ない検査法で注目された。

尾高ら(おゆみのクリニック)は大腸内視鏡検査における芍薬甘草湯注入法の有用性について報告した。本薬剤は平滑筋の鎮静・鎮痙作用を有し，生理食塩水を対照群とした比較試験で，腸管蠕動抑制による検査時間の短縮や被検者の苦痛軽減が得られることを示した。

水上ら(久里浜アルコール症センター)は有茎性ポリープの内視鏡摘除前に茎部にアンカークリップをかけておくと，摘除後の創部の結紮や縫合が容易になることを報告した。

小野寺ら(大宮医師会市民病院)は有茎性ポリープの内視鏡的摘除時に，やわらかい留置スネアで意図した部位を確実に絞扼するための手技の工夫について述べた。

吉田ら(九段坂病院)はESDを行う際の工夫として，右側結腸の処置困難例や反転観察例では，透視の併用が有効であることを示した。

玉井ら(慈恵医大)は大腸腫瘍の内視鏡的摘除後の潰瘍部を赤外線観察すると，露出血管の同定とともに的確なクリッピングが容易になることを示した。さらに赤外線観察非使用群より後出血率が低く，不要なクリッピングの防止にも有効であることを報告した。

岸原ら(癌研有明病院)は大腸内視鏡治療後の偶発症としてtransmural burn(TMB)に着目し，その発生頻度(0.03%)を示すとともに，病変の大きさや肉眼形態，摘除手技で発生頻度に差がないことを示した。さらにTMBの診断には炎症反応やCT所見に着目し，治療は腸管安静と抗生物質が有効であることを報告した。

いずれの発表も大腸内視鏡検査法や大腸腫瘍の内視鏡的摘除法の工夫として興味深いものばかりで，とくに炭酸ガス送気や芍薬甘草湯の注入法は被検者の苦痛軽減にも有効で注目された。実地臨床にすぐに活用できる発表が多く，会場の聴衆にとっても有意義なワークショップであったと考える。

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内視鏡手技における私の工夫(粘膜把持鉗子用チャンネル付き透明フードを用いるESD)

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吉井貴子　柳田直毅[2)] 亀田陽一

要旨：粘膜把持鉗子用チャンネル付き透明フードを使用した新たなESD手技に対して院内倫理委員会で承認を得，臨床使用して安全性と有用性を認めたため，本ESD補助具の使用方法(装着方，粘膜把持，カウンタートラクションのかけ方，二点固定)と直視下に血管および剝離部を捉えてのESD手技を提示することとした。把持した剝離粘膜口側を挙上・後方に押して剝離粘膜下組織に常時カウンタートラクションをかけながら，フックナイフの背側を剝離する粘膜下層に当てて通電するかアーム部を使用して連続剝離した。粘膜把持チェンネル付き透明フードの利点は，剝離操作において6時方向を透明フードで押さえ，11時方向から出る鉗子チャンネルより出した把持鉗子で切開した粘膜を把持して挙上・反転することにより，この二点で固定した剝離する粘膜下層にカウンタートラクションをかけることができ，同部位を8時方向のスコープ鉗子チャンネルから出したフックナイフで容易に剝離することができることである。

〔**Key Words**〕粘膜把持鉗子用チャンネル付き透明フード，ESD，早期胃癌

目　的

我々は内視鏡的粘膜下層剝離術(ESD)の安全・確実性と施行時間短縮を追及し，粘膜把持チャンネル付き透明フードを試作して動物実験を重ね安全性を確認した。このESD補助具を使用した新たなESD手技に対して院内倫理委員会で承認を得，臨床使用して安全性と有用性を認めたため，本ESD補助具の使用方法(装着方，粘膜把持，カウンタートラクションのかけ方，二点固定)と直視下に血管および剝離部を捉えてのESD手技を提示することとした。

方　法

症例は，胃体下部小彎後壁寄りの0－Ⅱa病変(A-Vmalformationの上に発育)と，胃前庭前部前壁の0－Ⅱc病変である。使用したスコープはウォータージェット機能を有するQ260J(OLYMPUS)，切開・剝離にはICC350(ERBE)を用いた。病変周囲に針状メスを使用してマーキングした。局注液はスベニール8倍希釈液(ボスミンとインジゴカルミン加)を用いた。病変周囲切開はスコープにショートタイプ透明キャップ(TOP)を装着して針状メスで行い，設定はオートカット80w，effect3とした。剝離には，現在は粘膜把持チャンネル付き透明フードとして市販されるようになったインパクトシューター（TOP)を用い(**Fig. 1**)，鉗子の出る位置をスコープの10時～11時に固定して，剝離粘膜把持には回転機能を有するホットクローを使用(**Fig. 2**)した。処置は，フックナイフを使用し，設定はforced40wとした。把持した剝離粘膜口側を挙上・後方に押して剝離粘膜下組織に常時カウンタートラクションをかけながら，フックナイフの背側を剝離する粘膜下層に当てて通電するかアーム部を使用して連続剝離した。細い血管の止血やプレ凝固にはフックナイフ(forced40w)，太い血管の止血やプレ凝固に対しては止血鉗子(ソフト凝固80w)を用いた。

成　績

症例1として提示したものは，胃体下部小彎後壁寄りの0－Ⅱa病変(**Color 1－a**)であり，A-

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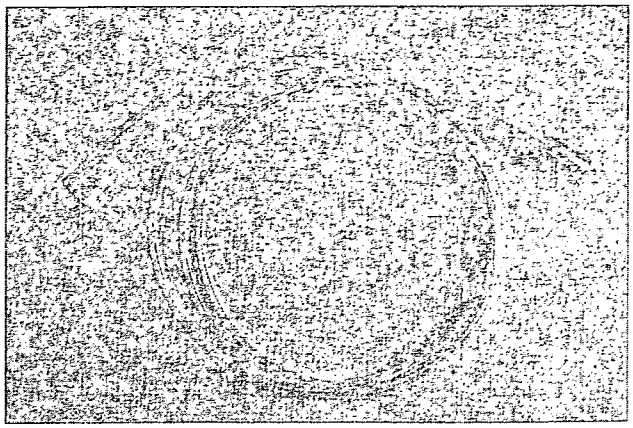

Fig. 1 Transparent hood with mucosa gripping channel attached.

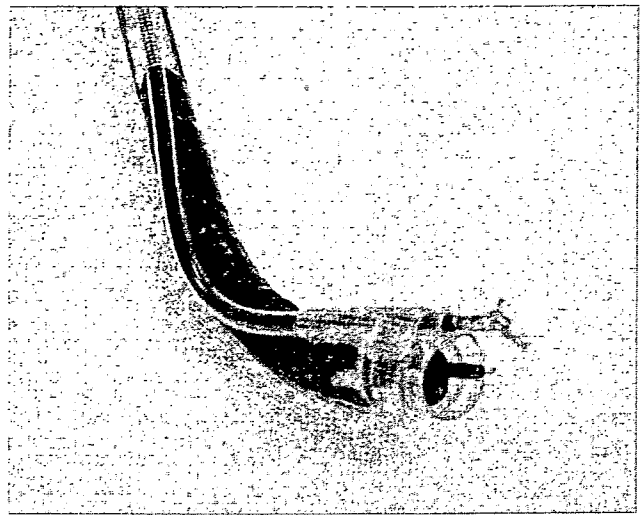

Fig. 2 New ESD assistive device, hot crow and hook knife were installed in endoscope.

Vmalformationと思われる動脈(穿通枝)の周囲を嚢状に拡張した静脈が絡みつくように発達していたが，粘膜を把持・挙上して剝離部を直視下に捉え，有効なカウンタートラクションがかけられたため(**Color 1-b**)，把持粘膜と異常血管の間の僅かな粘膜下組織にフックナイフの背側を当てて剝離を進めながら，止血鉗子で拡張した静脈の処理を行った。剝離後に拍動する動脈にクリッピングを施行した(**Color 1-c**)。

症例2として提示したのは，胃前庭前部前壁の0-Ⅱc病変(**Color 2-a**)であり，病変周囲切開後に粘膜口側を把持・挙上して剝離部を直視下に捉え，粘膜把持する位置を変えたり把持鉗子を出したりすることでカウンタートラクションをかけ続けて剝離を進めた(**Color 2-b**)。

我々の考案したデバイスを試用したESD手技は，粘膜剝離面を直視下に捉えられ，十分なカウンタートラクションをかけた状態で鉗子とフードの二点を使って剝離部を固定でき，止血や血管処理は容易，穿孔もなく剝離を安全かつ容易に施行することができた。

考　察

我々は動物実験を通して粘膜把持鉗子用チャンネル付き透明フードを開発し，これを臨床使用してその有用性を報告[1,2]して来た。ESDは画期的な内視鏡治療手技であるが，粘膜切除(EMR)と比べて一括切除率は格段に勝っているものの，手技に伴う出血や穿孔が多く切除時間も長い上に手技習得にも時間がかかるという問題[3~5]がある。我々がこの補助具を用いたESD手技を考案した理由は，このESDに伴うデメリットを改善するためには常時粘膜下層の剝離部を直視下に捉え，かつ有効なカウンタートラクションをかける必要があるからであった。

粘膜把持チェンネル付き透明フードの利点は，剝離操作において6時方向を透明フードで押さえ，11時方向から出る鉗子チャンネルより出した把持鉗子で切開した粘膜を把持して挙上・反転することにより，この二点で固定した剝離する粘膜下層にカウンタートラクションをかけることができ，同部位を8時方向のスコープ鉗子チャンネルから出したフックナイフで容易に剝離することができることである。この手技によって，①充分な視野を確保でき，②処置具と剝離部の距離を一定に固定可能となり，③血管処理や止血操作を容易に行なえ，④最後の粘膜剝離まで容易に同じ操作を持続することが可能になった。

結　論

粘膜把持鉗子用チャンネル付き透明フードを用いるESD手技は，非常に有用性が高いだけでなく安全かつ簡便であり，ESDの新たな手法の一つとなり得るものと思われる。

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〈カラーは1頁に掲載〉

An ESD procedure using transparent hood with muscosa gripping channel attached

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原著

食道ESD手技における粘膜把持鉗子用チャンネル付き透明フードの有用性—実験的検討—

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要旨：内視鏡的食道粘膜下層剝離術（endoscopic submucosal dissection：ESD）に求められる安全性・確実性・簡便性の向上と施行時間短縮を追及し，粘膜把持鉗子用チャンネル付き透明フードを試作した．雑犬を使用した動物実験で，このデバイスを使用したESDを施行する群と透明フードのみを使用した従来のESDを施行する群を比較検討した．

結果として，この補助器具使用による利点は，①剝離粘膜を把持し挙上させ，さらに反転させて後方に押すことで，粘膜剝離面を直視下に観察することがより容易となり，止血および血管処理が容易となっただけでなく穿孔の危険性もなくした．②剝離面の粘膜下組織に確実なカウンタートラクションをかけることができ，剝離時間を短縮した．特に，③この切開粘膜把持と切開粘膜口側にフードを接着させる操作は，呼吸や拍動の影響を減じ，剝離部と処置具の距離を一定とし，安全な食道粘膜剝離操作を可能にした．

動物実験から粘膜把持鉗子用チャンネル付き透明フードは食道のESDに有用な補助具であり，臨床使用においても同様の有用性が期待される．

Key words　食道ESD（内視鏡的粘膜下層剝離術）／粘膜把持鉗子用チャンネル付き透明フード／カウンタートラクション

I　目　的

われわれは，2003年よりESDを動物実験で施行し始め，2004年より臨床に取り入れ始めてはいるものの，出血等の偶発症が多く，EMR法と比較して切除時間が長いなどESDの問題点[1),2)]を痛感してきた．ESDの普及を躊躇させるこれらの問題点を解決するだけでなく，様々な利点を有するESD補助器具としての粘膜把持鉗子用チャンネル付き透明フードを試作し，動物実験からその使用法を考案して有用性を確認，早期胃癌症例に臨床応用してその有用性を確認したため報告[3),4)]してきた．

今回は，食道早期癌に対するESDとして本法を施行するにあたり，動物実験を施行して安全性および有用性を確認したため報告する．

II　方　法

動物実験：体重8～15 kg，雑種成犬6匹を使用した．実験24時間前より絶食を行い，水は自由に与えた．本実験は北里大学実験動物指針に基づいて行った．チオペンタール・ナトリウム25 mg/kgを静注して麻酔導入を行った．気管内挿管し，酸素と笑気1：1の混合気を使用，ハーバードレスピレーションポンプによって呼吸管理（20回/分）を行い，麻酔維持はフローセン1.5%を用いた．使用した内視鏡機器はオリンパス社製Q20で，

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Osamu MOTOHASHI
Utility of an ESD Procedure of Esophagus using Assistive Device (Transparent Hood with Mucosa Gripping Channel Attached) (An Examination of Animal Studies).

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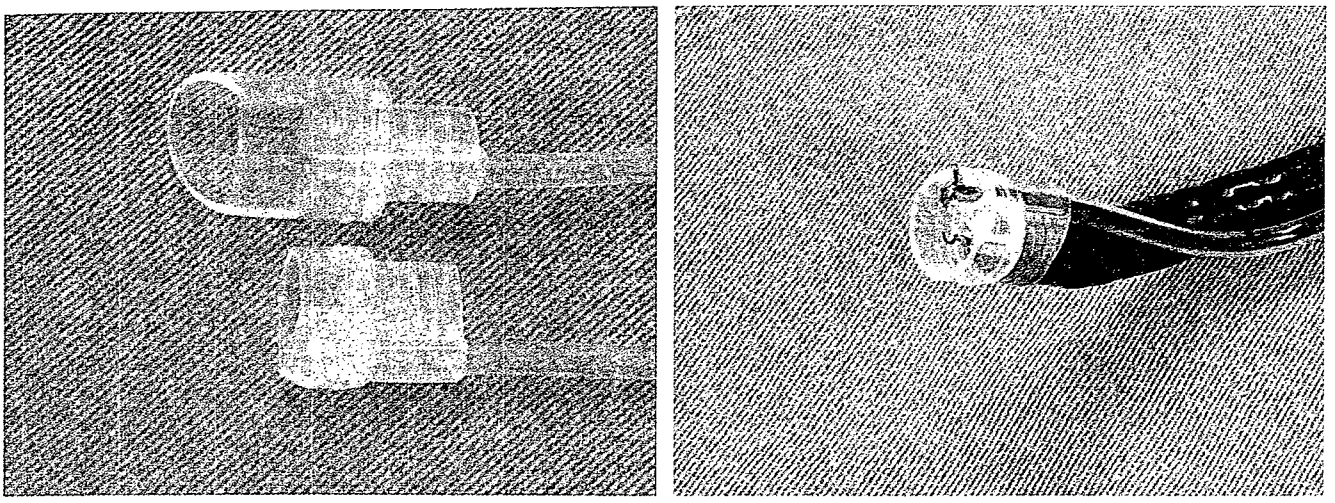
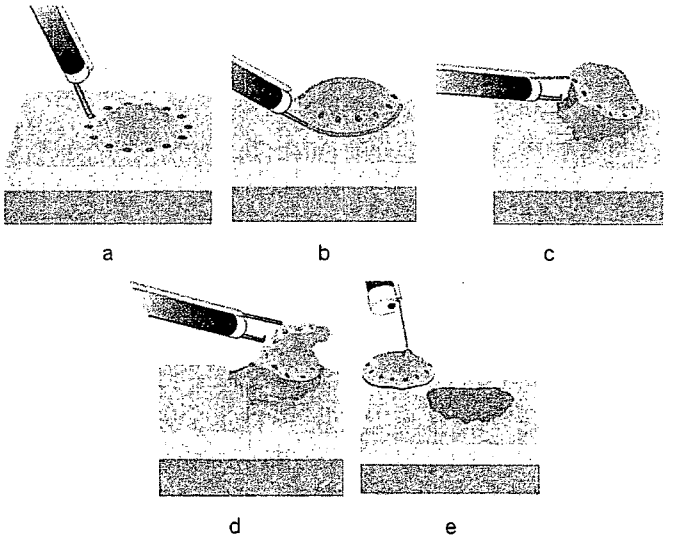


a　b

Figure 1　斜型アスピレーションムコゼクター（クリエートメディック）を使用した粘膜把持鉗子用チャンネル付き透明フード．
a：アスピレーションムコゼクターと平坦にカットしたデバイス．
b：粘膜把持鉗子用チャンネル付き透明フードに把持鉗子とフックナイフを装着．



a　b　c　d　e

Figure 2
a：針状メスで病変周囲マーキング．
b：スベニール希釈液粘膜下局注後，病変周囲切開．
c：把持鉗子で粘膜把持・挙上，フードで口側固定しカウンタートラクションをかけ，フックナイフで粘膜下層剝離．
d：剝離が進むにつれ把持した粘膜口側を挙上させ後方に押して，剝離してゆく粘膜下組織にカウンタートラクションをかけ剝離を続ける．
e：粘膜剝離終了，粘膜把持したまま回収．

CCD カメラ (OLYMPUS) を装着した．高周波発生装置は ERBE ICC200 (ERBE) を用いた．(切開は Auto cut 80w，effect3，剝離には Forced 40 w，止血操作は Forced 40w か止血鉗子の使用時にはソフト凝固 60w を使用した．) 雑種成犬 6 匹，各 3 部位（下部食道・中部食道・上部食道）の計 18 部位：A 群．ショートタイプ透明円筒型フード (OLYMPUS) を使用した通常の ESD を 6 部位に，B 群．Figure 1 に示すようにシリコン性の斜型アスピレーションムコゼクター（クリエートメディック）の先端部を切ったものを粘膜把持鉗子用チャンネル付き透明フードとして使用した ESD を 12 部位に施行して比較検討した．内視鏡への本フードの装着は，内視鏡の鉗子口 8 時に対して鉗子用チャンネルが 10-11 時になるようにし，フードとチューブの部分はテープで内視鏡に固定した．把持鉗子として，把持部分の短さと粘膜を上下で確実に把持するために回転機能を有するホットクロー (OLYMPUS) を用いた．

A 群 B 群とも，針状メスで切除予定粘膜に直径 25 mm のマーキングを行い，大きさに関して偏りがないようにした．粘膜下の局注にはグリセオール（インジゴカルミン 0.04 mg/ml 加）を使用した．ESD の周囲切開は針状メス (Auto cut 80w・effect3) で施行，粘膜下層剝離にはフックナイフ (Forced 40w) を使用し，剝離法は小山ら[5]の方法に準じて粘膜下層組織をフック部で引っ掛け手前に引きながら通電，剝離した．

B 群における手技の模式図を Figure 2 に示す．剝離時は，粘膜把持チャンネルから出した鉗子で把持した剝離粘膜口側を挙上させ後方に押して，剝離してゆく粘膜下組織にカウンタートラクションをかけると同時に，キャップを近接させて直視下に捕らえ，フックナイフを用いて剝離する．剝離法は，カウンタートラクションをかけた粘膜下層組織に対しフックナイフのフックの背側を固有

Table 1　ESD（透明フード使用）と粘膜把持鉗子用チャンネル付き透明フードを使用した食道ESDの比較（動物実験による検討）.

	A群：ESD（透明フード）n＝6	B群：ESD(粘膜把持鉗子用チャンネル付き透明フード)　n＝12	有意差（Student t検定）
施行時間（分）	116.17±16.00 平均値±標準偏差	79.00±11.39 平均値±標準偏差	p＜0.05 有意差あり
止血操作（回）	5.33±1.51	2.67±1.07	p＜0.05
止血時間（秒）	67.50±9.35	34.41±14.57	p＜0.05
剝離時ブラインド率（%）	39.33±6.65	0.00±0.00	p＜0.05
穿孔（回）	1（pin hole）	0	

Table 2　透明フード使用（1点固定）と粘膜把持鉗子用チャンネル付き透明フード使用（2点固定）した食道ESDにおける呼吸性変動および抑制率の比較（動物実験による検討）.

	A群：ESD（透明フード）n＝6	B群：ESD(粘膜把持鉗子用チャンネル付き透明フード)　n＝12	有意差(A群1点固定変動 vs. B群2点固定変動)（Student t検定）
固定前変動（mm）	6.17±0.75	5.83±0.89	
1点固定変動（mm）	1.83±0.41	1.98±0.57	
変動抑制率（%）	70.4±4.34	66.29±6.66	
有意差（固定前 vs. 1点）（Student t検定）	p＜0.05 有意差あり	p＜0.05 有意差あり	
2点固定変動（mm）		0.43±0.25	p＜0.05
変動抑制率（%）		92.78±3.61	有意差あり
有意差（固定前 vs. 2点）（Student t検定）		p＜0.05 有意差あり	

右側の有意差検定は，A群1点固定による変動（A群網掛け部）とB群2点固定による変動（B群網掛け部）との間のものである.

筋層と平行に軽く当てて通電するもので，組織をフックすることなく容易に剝離可能である．連続して剝離する場合には，アームカットを施行した．出血や処理すべき血管は直視下に観察し，フックナイフ（フォースト40w）または止血鉗子（ソフト凝固60w）で出血点や血管を処理した．二群間の比較検討はESD施行時間，止血操作回数，止血時間，呼吸性変動抑制率および粘膜剝離時直視下に剝離部を捉えられない時間の割合（ブラインド率）で比較検討し，統計学的有意差検定としてStudent t検定を使用した．呼吸性変動抑制率は，ゴム風船で作成したメジャーを挿入し，フード接着（1点固定）およびフード接着と粘膜把持（2点固定）する前の食道壁呼気時の目盛と吸気時の目盛の差と剝離時（A群では粘膜へのフード接着のみ，B群ではフード接着のみと把持とフード接着による2点固定）の食道壁呼気時の目盛と吸気時の目盛の差を測定することによって算出した．また，呼吸性変動抑制に対する有意差検定は，A群の症例ではフードのみとB群の症例ではフード（把持なし）およびフードと把持による二点固定時と，おのおの固定前変動との間で行なった．さらに，A群1点固定による変動とB群2点固定による変動との間でも，二群間の有意差検定を行なった．

III　結　果

動物実験：雑犬の食道粘膜下層の結合組織はヒトとは異なり密であるため，ヒトほど容易にlifting しません．このため，局注・切開・剝離ともに時間がかかることになりフードをもぐらせる剝離に時間がかかり，粘膜翻転・出血点確認・剝離粘膜のカウンタートラクションは，Table 1，2で示すようにA群は不十分であり，穿孔が1例に見られ，止血操作の遅れにつながった．一方，B群では，局注・切開に関してはA群と同様に時間はか

かるものの，8例とも剝離粘膜のカウンタートラクションは良好であり，穿孔は見られず出血点は全例確認でき止血操作の遅れもなかった．また，フードの粘膜接着により一点のみで固定するA群では全例，呼吸性変動による食道の動きを70%程しか抑えられず，食道壁の動き（呼吸）に合わせて処置具の出し入れを微調整する必要が生じたが，これと比べて粘膜把持とフードの接着の2点で固定を行うB群では，2点間の粘膜下層剝離部に対し，呼吸性変動を90%強抑えることができ，処置部の動きを最小に抑えることで粘膜剝離を安全に施行することができた．ESD施行時間は，A群で平均2時間であったが，B群では平均80分（最短で60分，最長でも88分）であった．両群の比較検討で，B群では切開・剝離に要した施行時間は短く，止血回数の少なさおよび止血鉗子を使用した止血時間の短さ，食道壁の呼吸性変動抑制率は大きく，全て両群間に有意差を認めた．また，剝離操作を通して剝離する部位を直視下に捉えられない割合（ブラインド率）は0%でありこれも有意差を認めた．病理標本の所見では，両群ともに粘膜下層での十分な切除となっていた．心拍動の影響は食道の管腔内側に上下する動きであり，定量しての比較が困難だったため検討しなかったが，鉗子による把持とフードの接着による2点固定の間の処置部は呼吸性変動と同等に，ほぼ完全に動きを抑えることができた．

IV 考　按

われわれは動物実験でESDの訓練を繰り返した後，二年前よりESDを直径20 mm以上の早期胃癌病変に施行してきた．この実験と臨床でのESD施行症例を検討した結果，現在行なわれているESDの改善点は，手技全体を通して剝離面を定常的かつ十分に観察できない，剝離する粘膜下層組織に十分なカウンタートラクションをかけられない，処置具と切開・剝離部の距離を保持することができない点であることが判明した．これらの点を克服し，安全で確実，さらに従来法より短時間で施行可能なESD手技確立のため，粘膜把持鉗子用チャンネル付き透明フードを試作し，院内の倫理委員会の承認を得て，2005年12月より早期胃癌症例に施行し良好な成績を得て，これを報告してきた．今回はさらに動物実験を重ね，食道のESDに対しても本法が非常に有用な手技であることが判明したため，実験結果とともに報告することとした．

現在までいろいろな食道のESD処置具・補助具・切除法が開発[5)~8)]されてきたが，前記の改善点すべてを満足するには至っていない．視野を確保し，出血点を確認，カウンタートラクションをかけて粘膜剝離を進めるため，先端フードが用いられ，切開直後の剝離面に入り込むにはSTフード(Small caliber-tip Transparent Hood)[6)]が使用されるものの，どちらも剝離部に押し付けて処置をするために視野が狭くなるという問題が残る．これに反して，われわれの粘膜把持鉗子用チャンネル付き透明フードは，通常の内視鏡に装着するだけで，粘膜切開直後から把持鉗子で粘膜剝離面を広げて十分な視野を確保することが可能であり，出血点や予防的に凝固する血管の観察を容易に行える．また，本法では把持した粘膜の下層どこからでも剝離を始められ，フードを直接押し付けてのカウンタートラクションだけでなく，鉗子で剝離粘膜の手前側を把持して後方に押す（把持鉗子を出す）だけで粘膜は翻転し十分な視野と剝離部との一定の距離が得られ，これから剝離する粘膜下組織に充分なカウンタートラクションがかけられることから，安全・容易に剝離が可能である．さらに食道では特に重要な点であるが，小山らが報告[8)]しているようにフックナイフは呼吸性変動に合わせて使用する必要があった．これに対して本法は，剝離粘膜を鉗子で把持して先端フード縁を粘膜に接着させる二点固定することによって，剝離に用いる処置具と剝離部位との距離を一定にして呼吸性変動および拍動による食道壁の動きを抑制するという利点も見られる．

今回，実験で用いた粘膜把持鉗子用チャンネル付き透明フードは，シリコン性の斜型アスピレーションムコゼクター（クリエートメディック）の先端部を切ったものを使用している．本デバイスは，Q260J (OLYMPUS) に装着すると，デバイスの鉗子用チャンネル（把持鉗子）とQ260Jの鉗子口（処置具）およびQ260Jのウオータージェットを使用することが可能となり，ESDで必要な機能が満たされることになる．

また，われわれが用いたフックナイフのアームの背側を固有筋層と平行に滑らせるアームカット

による安全な連続剥離を可能としたのも粘膜把持鉗子用チャンネル付き透明フードを使用したからである．粘膜を把持しているために剥離距離（フックナイフの動き）に制限がかかり，ナイフが滑り誤って切りすぎることが無いためである．

本手技は把持鉗子10-11時，フードによる接着6時の2点で保持し，この2点間の常時カウンタートラクションをかけられた粘膜下層を8時方向から出すフックナイフで剥離していくというものであり，常にこの位置をキープすることを原則とする．また，スコープのシャフトを捻ることで接着した6時の粘膜と把持部の位置は保たれ，その中間に位置する粘膜下層にフックナイフが当たることになる．また，把持した粘膜はいつまでも同じ位置を把持するのではなく，中央把持の剥離のみではなく，右側辺縁を剥離する時は右側寄りに把持し直し，左側辺縁が剥離しづらければ左側寄りを把持して剥離を進め，大きな剥離粘膜が邪魔になるときは辺縁ではなく剥離された粘膜の剥離面を3時－9時に向けた把持鉗子で把持することで常時同じ調子で剥離が行なえ，スコープ操作の制限を解除することができることになる．つまり，剥離してゆく部位に応じて把持する部位を変えることを心がけることが重要となる．

今回の実験から，ESD手技を安全・確実・短時間で施行でき得る粘膜把持鉗子用チャンネル付き透明フードは食道のESDにおける有用な補助具であることが明らかとなった．われわれは，さらなる実験と症例を重ねて安全で確実なESD手技の確立を目指すつもりである．

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UTILITY OF AN ESD PROCEDURE OF ESOPHAGUS USING ASSISTIVE DEVICE (TRANSPARENT HOOD WITH MUCOSA GRIPPING CHANNEL ATTACHED) (AN EXAMINATION OF ANIMAL STUDIES)

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In pursuit of shortoning of procedure time and a safty and convenient improvement in endoscopic submucosal dissection (ESD) of esophagus, we experimentally produced a transparent hood with a mucosa gripping channel attached. An examination of animal studies using mongrel dogs was done. We compared a group to enforce ESD which used this device with a group to enforce conventional ESD which used only a transparent hood and reviewed it.

The use of this assistive device has the following advantages. ① By lifting the separated mucosa, then reversing and pressing it backword, the mucosa-stripped plane can be observed under direct vision. This procedure not only makes hemostasis and blood vessel processing easy, but also perforation difficult to be occurred. ② Reliable counter-traction can be applied to the submucosal tissue of the stripped plane, and separation time could be shortened. ③ Especially this method of gripping the excised mucosa and attaching the hood to the opening side of the excised reduces the effects of respiration and pulsation, keeps the distance of the separated part and instrument constant and enables safe separation procedure of esophagus.

Its utility was confirmed in animal experiments, and it can be expected similar utility in clinical application.

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ORIGINAL ARTICLE

A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer

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Abstract
Purpose The aim of this study was to assess the efficacy and toxicity of weekly irinotecan in patients with metastatic pancreatic cancer.
Patients and methods Patients with histologically proven pancreatic adenocarcinoma, at least one bidimensionally measurable metastatic lesion, and no prior chemotherapy were selected. Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. Pharmacokinetics was examined on day 1 of the first cycle of treatment.
Results Thirty-seven of 40 enrolled patients were assessable for efficacy and toxicity. A partial response was obtained in 10 patients, giving an overall response rate of 27.0% (95% confidence interval 13.8–44.1%). The median overall survival was 7.3 months with a 1-year survival rate of 29.5%. Although toxicities were generally tolerated, one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. Pharmacokinetic study showed that patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.
Conclusion Single-agent irinotecan has significant efficacy for metastatic pancreatic cancer. The toxicity with this schedule appears manageable, though it must be monitored carefully.

Keywords Irinotecan · Phase II study · Pancreatic cancer · Chemotherapy · Pharmacokinetics

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Introduction

Pancreatic cancer is a highly aggressive disease, with approximately 21,000 deaths annually in Japan [7]. While surgery remains the only potential curative option for this disease, the vast majority of patients unfortunately present with advanced, unresectable disease. Although it has been demonstrated that gemcitabine is

an effective tool for palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer [2], single-agent gemcitabine has shown limited benefit, with objective response rates of less than 15% and a median overall survival of around 4–6 months [2, 4, 5]. Therefore, there is a clear need to identify a new effective chemotherapeutic regimen for pancreatic cancer.

Irinotecan is a water-soluble semisynthetic derivative of camptothecin, a plant alkaloid obtained from the *Camptotheca acuminata* tree. Irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), bind to topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing double-stranded DNA breaks and consequent tumor cell death. Irinotecan is internationally approved for use in metastatic colorectal cancer, and has broad activity against other malignancies including lung cancer [6, 9, 15, 16]. Although several studies of single-agent irinotecan or irinotecan-based chemotherapy against pancreatic cancer have been reported [11, 12, 14, 18, 22], the role of irinotecan in the treatment of patients with pancreatic cancer remains unclear yet. Because there are few effective agents for pancreatic cancer to date, it is important to determine the clinical efficacy of irinotecan for this disease. We, therefore, conducted an open-label, multicenter, single-arm phase II study to evaluate the efficacy and toxicity of single-agent irinotecan in patients with pancreatic cancer. In the current study, we adopted weekly administration of irinotecan because safety of this schedule has been confirmed in other cancers in Japan [6, 9, 16]. Since patients with pancreatic cancer tend to suffer various tumor-related complications such as obstructive jaundice and impaired liver function, pharmacokinetic study was also performed.

Patients and methods

Patient selection

Patients were entered into the study if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; at least one bidimensionally measurable metastatic lesion; no history of prior chemotherapy or radiotherapy; age 20–74 years; Karnofsky performance status (KPS) ≥ 50 points; estimated life expectancy ≥ 2 months; adequate bone marrow function (WBC count $< 12{,}000$ per mm^3, neutrophil count $\geq 2{,}000$ per mm^3, platelet count $\geq 100{,}000$ per mm^3, and hemoglobin level ≥ 10.0 g/dl), adequate renal function (serum creatinine and blood urea nitrogen level $\leq$ the institutional upper limit of normal), and adequate liver function (serum total bilirubin level ≤ 2.0 mg/dl, serum transaminases levels ≤ 2.5 times the institutional upper limit of normal); and written informed consent. Patients were excluded if there was a history of severe drug hypersensitivity; serious complications; central nervous system metastases; other concomitant malignant disease; marked pleural or peritoneal effusion; and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board of each participating center, and conducted in accordance with Good clinical practice guideline in Japan.

Treatment plan

This study was an open-label, multicenter, single-arm phase II study. Irinotecan was supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsha Co., Ltd. (Tokyo, Japan). Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue. Prophylactic administration of antiemetic agents was allowed at the investigator's discretion. Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during treatments. If patients experienced neutropenia of $< 1{,}500$ per mm^3, thrombocytopenia of $< 100{,}000$ per mm^3, fever (≥ 38°C) with suspected infection, grade ≥ 1 or watery diarrhea, or $\geq$ grade 3 non-hematological toxicities other than nausea, vomiting and anorexia, irinotecan administration was omitted on that day and postponed to the next scheduled treatment day. If patients experienced neutropenia of < 500 per mm^3, thrombocytopenia of $< 50{,}000$ per mm^3, fever (≥ 38°C) with suspected infection, or grade ≥ 2 or watery diarrhea at any time, the irinotecan dose of the subsequent cycle was reduced by 20 mg/m^2. Patients went off study if they required more than two dose reductions. If the next cycle could not start within 4 weeks from the scheduled day, the patient was withdrawn from the study. The toxicity of irinotecan therapy was evaluated according to the National Cancer Institute Common Toxicity criteria version 2.0.

Evaluation

Objective tumor response was evaluated every 4 weeks according to the Japan Society for Cancer Therapy (JSCT) criteria [8], which is similar to the WHO crite-

ria. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. A partial response (PR) was defined as a $\geq$ 50% reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. No change (NC) was defined as a < 50% reduction or a < 25% increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. Progressive disease (PD) was defined as a $\geq$ 25% increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [1]. Objective tumor response was secondarily assessed according to the response evaluation criteria in solid tumors (RECIST criteria) [20] among patients with at least one measurable metastatic lesion whose longest diameter measured by CT is no less than double the slice thickness. An external review committee confirmed objective responses and toxicities.

Clinical benefit was evaluated on the basis of established criteria [13]. Each patient was classified as a clinical benefit responder or non-responder on the basis of the change in two parameters of clinical benefit (pain and KPS). In the current study, the body weight was not used to evaluate clinical benefit response because the body weight of patients with pancreatic cancer sometimes increases due to not only improvement of their condition but also retention of malignant ascites. A positive response for pain was defined as an improved pain intensity of $\geq$ 50% from baseline for $\geq$ 4 weeks, or a decreased morphine consumption of $\geq$ 50% from baseline for $\geq$ 4 weeks. A positive response for KPS was defined as an improved KPS of $\geq$ 20 points from baseline for $\geq$ 4 weeks. To be classified as a clinical benefit responder, a patient had to achieve a positive response in at least one parameter (pain or KPS) without being negative for the other, sustained for $\geq$ 4 weeks.

Pharmacokinetics

To investigate the impact of biliary drainage on pharmacokinetics of irinotecan, we planned to recruit five patients each with and without biliary drainage. Heparinized blood samples (5 ml) for the pharmacokinetic study were obtained before infusion of irinotecan, at the end of the 90 min infusion, and 0.5, 1, 2, 4, 6, 8, 24 h after the completion of infusion on day 1 of the first cycle. Blood samples were immediately centrifuged at 3,000 rpm for 10 min to remove plasma and stored in polyethylene tubes at −20°C until analysis. Quantitative analysis of total irinotecan and its metabolites, SN-38, SN-38 glucuronide, and 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) was performed by methods previously described [17, 19].

Statistical analysis

The primary goal was to evaluate the response rate (CR and PR) of irinotecan. The 95% confidence interval for response rate was calculated based on the binomial distribution. The response duration was defined as the interval from the first documentation of response to the first documentation of tumor progression. The time to progression (TTP) was calculated from the date of study enrollment to the first documentation of tumor progression; and overall survival was calculated from the date of study enrollment to the date of death or the last follow-up with censored value. Median overall survival and the median TTP were estimated by the Kaplan–Meier method and 95% confidence interval were estimated based on the Greenwood's formula. A total of 35 patients were planned to be enrolled based on the assumptions that the expected response rate of irinotecan was 15% and the threshold rate was 5%. A two-stage design was used in this study. The interim analysis was planned when 15 patients were enrolled in the first stage of the study. If the upper limit of the 90% confidence interval (one-sided) did not exceed the expected rate of 15% (no objective response in the 15 patients), irinotecan was judged to be ineffective and the study was ended. If an objective response was observed in any of the first 15 patients, additional 20 patients were enrolled in the second stage of accrual to estimate the response rate. If 6 or more out of 35 patients achieved objective response, the lower limit of the 95% confidence interval (two-sided) exceeds the threshold rate of 5%, and then the agent would be considered to be active for metastatic pancreatic cancer.

Results

Patients

Forty patients were enrolled in the study by 7 institutions between August 2001 and November 2002. Of the 40 patients, 3 patients who did not receive irinotecan because of rapid tumor progression or protocol violation were excluded from analysis. Patient characteristics of the remaining 37 patients are listed in Table 1.

All 37 patients had metastatic disease and had a good KPS of ≥ 80. Morphine was prescribed for 10 patients due to abdominal or back pain and 14 patients were assessable for clinical benefit response. Seven patients had recurrent disease after pancreatic resection. Two patients underwent percutaneous transhepatic biliary drainage for obstructive jaundice prior to study enrollment.

Treatments

Data were collected through May 4, 2004, providing 18 months of survival follow-up from the time accrual ended. Thirty-seven patients were given a total of 108 cycles of therapy, with a median of 2 cycles each (range 1–10). The administration of irinotecan on day 8 and day 15 was performed in 87 (80.6%) and 76 (70.4%) of 108 cycles, respectively. Dose reduction was required in 13 patients (35.1%), mainly due to diarrhea and fever with suspected infection. At the time of analysis, all patients had discontinued the study because of disease progression ($n = 28$), toxicity ($n = 5$), treatment-related death ($n = 1$), and withdrawal of consent due to other reasons ($n = 3$). After discontinuation of irinotecan, 26 patients received gemcitabine monotherapy or gemcitabine-based combination therapy; one patient was treated with S-1, and remaining 10 patients underwent only supportive care. Among 27 patients treated with second-line chemotherapy, 2 patients who received gemcitabine monotherapy achieved a PR.

Table 1 Patient characteristics ($n = 37$)

Characteristics		No. of patients (%)
Gender		
Male		25 (67.6)
Female		12 (32.4)
Median age, years (range)	59 (41–74)	
Karnofsky performance status, point		
100		8 (21.6)
90		25 (67.6)
80		4 (10.8)
Median body surface area (m^2) (range)	1.55 (1.31–1.85)	
History of surgical resection		7 (18.9)
PTBD		2 (5.4)
Sites of metastasis		
Liver		33 (89.2)
Lymph nodes		17 (45.9)
Lung		8 (21.6)
Others		3 (8.1)

PTBD percutaneous transhepatic biliary drainage

Efficacy

Of 37 patients, 10 patients achieved a PR according to the JSCT criteria (Table 2). The overall response rate was therefore 27.0% (95% confidence interval 13.8–44.1%) with median response duration of 4.1 months (range 0.9–7.1 months). The median TTP was 2.1 months (range 0.7–9.5 months), and the median overall survival of 7.3 months (range 0.7–25.9 months) with a 1-year survival rate of 29.5% (Fig. 1). Of 29 patients assessable for RECIST criteria, a PR was seen in 8 patients (27.6%), stable disease in 6 patients (20.7%), and PD in 12 patients (41.4%). With regard to clinical benefit, 2 of 14 evaluable patients had pain relief and were classified as a responder (Table 3).

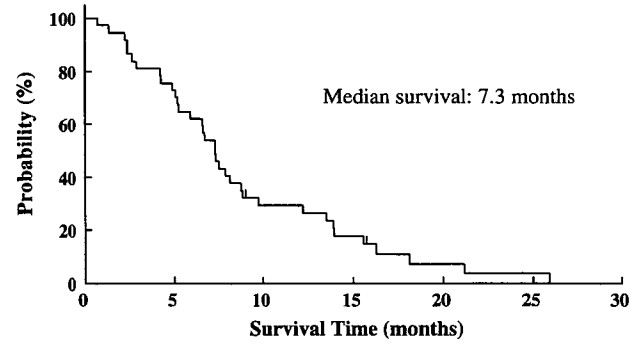

Fig. 1 Overall survival curve of all 37 patients

Table 2 Efficacy results

	No. ($N = 37$)	%
Tumor response		
Partial response	10	27.0
No change	7	18.9
Progressive disease	17	45.9
Not evaluable	3	8.1
Time to progression (months)		
Median	2.1	
Range	0.7–9.5	
Overall survival (months)		
Median	7.3	
Range	0.7–25.9	
1-year survival rate		29.5

Table 3 Clinical benefit response ($n = 14$)

		Karnofsky performance status		
		Improved	Stable	Worse
Pain	Improved	0	2	0
	Stable	0	6	1
	Worse	0	5	0

Toxicity

All 37 patients were assessable for toxicity. The major toxicities observed during the study are summarized in Table 4. The most common toxicities were hematological toxicity and gastrointestinal toxicity. Grade 3 or 4 neutropenia occurred in 10 patients (27.0%) and 5 patients received granulocyte-colony stimulating factors. The neutrophil count nadir typically occurred on day 21, and recovered to baseline values by day 28. Although nausea, vomiting, and anorexia were observed frequently, most of these toxicities recovered spontaneously or with adequate supportive treatment. Grade 3 diarrhea occurred in four patients and they were treated with loperamide. Most diarrheas appeared during the first cycle of treatment: the median time to the worst day of diarrhea was 13 days from the initiation of a cycle of therapy. Though the toxicities were mild to moderate in severity and short in duration, one patient died at day 21 of the first cycle of treatment because of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and watery diarrhea due to irinotecan. The patient, a 58-year old woman with pretreatment KPS of 100, developed grade 4 neutropenia on day 12 complicated by fever (38.8°C) and grade 3 diarrhea that evolved to fatal shock despite aggressive medical management.

Table 4 Treatment-related adverse events ($n = 37$): worst grade reported during treatment period

Toxicity	Grade				Grade 1–4 (%)	Grade 3–4 (%)
	1	2	3	4		
Hematologic						
Leukopenia	15	6	8	1	81.1	24.3
Neutropenia	5	11	8	2	70.3	27.0
Anemia	0	14	3	0	45.9	8.1
Thrombocytopenia	1	1	1	1	10.8	5.4
Non-hematologic						
Nausea	7	12	15	–	91.9	40.5
Vomiting	7	14	5	0	70.3	13.5
Diarrhea	15	8	4	0	73.0	10.8
Constipation	1	8	2	0	29.7	5.4
Anorexia	4	7	14	1	70.3	40.5
Stomatitis	2	0	0	0	5.4	0
Rash	1	0	0	0	2.7	0
Alopecia	24	1	–	–	67.6	–
Fatigue	3	8	1	1	35.1	5.4
Fever	3	1	0	0	10.8	0
Infection	2	1	4	1	21.6	13.5
Total bilirubin	4	1	1	0	16.2	2.7
AST	5	5	2	0	32.4	5.4
ALT	4	4	3	0	29.7	8.1
Hyponatremia	6	0	3	0	24.3	8.1
Creatinine	0	0	2	0	5.4	5.4

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Pharmacokinetics

A pharmacokinetic analysis was performed in five patients without biliary drainage and in two patients who underwent percutaneous transhepatic biliary drainage (Planned five patients could not be enrolled in drainage group because only two patients had biliary drainage in the current study). Table 5 and Fig. 2 show the pharmacokinetic parameters for irinotecan and its three major metabolites in patients with and without biliary drainage. Although it was difficult to assess the influence of biliary drainage in this study because of the small number of subjects analyzed, patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.

Discussion

The prognosis of the patients with pancreatic cancer remains poor even after a randomized study demonstrated survival advantage of gemcitabine against advanced pancreatic cancer, indicating necessity of new effective agents or combination regimens for this dismal disease. Irinotecan, which has a quite different mechanism from gemcitabine, has been considered one of the attractive agents for pancreatic cancer, since this agent has demonstrated substantial activity in various types of malignant tumor [6, 9, 15, 16]. The current multicenter phase II study was, therefore, conducted to evaluate the efficacy and toxicity of single-agent irinotecan in patients with metastatic pancreatic cancer.

In this study, we found that weekly irinotecan demonstrated a good overall response rate of 27.0% in 37 patients with metastatic pancreatic cancer. In addition, a relatively long median overall survival of 7.3 months was shown, though all patients in our study had metastatic disease. As to clinical benefit response, 2 of 14 patients achieved clinical benefit response. These results indicate that irinotecan has a substantial antitumor effect on pancreatic cancer.

The major toxicities of irinotecan that were seen in the study were myelosuppression and gastrointestinal toxicities, similar to the previous observation of irinotecan monotherapy in other cancers [6, 9, 16]. Most toxicity was mild to moderate, and manageable with conservative treatment. However, one patient died of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and diarrhea. Pretreatment condition of this patient was good (KPS = 100), and it was difficult to predict these