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ORIGINAL REPORT

Randomized Phase III Study of Gemcitabine Plus S-1, S-1 Alone, or Gemcitabine Alone in Patients With Locally Advanced and Metastatic Pancreatic Cancer in Japan and Taiwan: GEST Study

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See accompanying editorial on page 1621

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ABSTRACT

Purpose
The present phase III study was designed to investigate the noninferiority of S-1 alone and superiority of gemcitabine plus S-1 compared with gemcitabine alone with respect to overall survival.

Patients and Methods
The participants were chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive only gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle), only S-1 (80, 100, or 120 mg/d according to body-surface area on days 1 through 28 of a 42-day cycle), or gemcitabine plus S-1 (gemcitabine 1,000 mg/m^2 on days 1 and 8 plus S-1 60, 80, or 100 mg/d according to body-surface area on days 1 through 14 of a 21-day cycle).

Results
In the total of 834 enrolled patients, median overall survival was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The noninferiority of S-1 to gemcitabine was demonstrated (hazard ratio, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority), whereas the superiority of gemcitabine plus S-1 was not (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$). All treatments were generally well tolerated, although hematologic and GI toxicities were more severe in the gemcitabine plus S-1 group than in the gemcitabine group.

Conclusion
Monotherapy with S-1 demonstrated noninferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer.

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INTRODUCTION

Pancreatic cancer (PC) is currently the eighth leading cause of cancer-related mortality worldwide, with an estimated 266,000 deaths in 2008.[1] Gemcitabine became the standard treatment for advanced PC, improving overall survival (OS) compared with fluorouracil.[2] Although various gemcitabine-based combination regimens have been evaluated, only erlotinib added to gemcitabine showed a survival benefit over gemcitabine, and that was marginal.[3]

Fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX), a gemcitabine-free combination regimen, has recently demonstrated a clear survival benefit compared with gemcitabine for patients with metastatic PC who have a performance status of 0 to 1.[4] However, because FOLFIRINOX is associated with significant toxicity, this regimen must be limited to patients with good performance status and requires close monitoring.[5]

In Japan, clinical trials of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with PC. S-1

is an oral fluoropyrimidine derivative shown to be effective for gastric and various other types of cancers.[6,7] Phase II studies of S-1 as first-line therapy for metastatic PC resulted in good response rates of 21.1% to 37.5%.[8,9] Consequently, S-1 was approved for the indication of PC in Japan in 2006. Development of gemcitabine plus S-1 (GS) studies have also been initiated, mainly in Japan, and two phase II studies reported high response rates of 44.4% to 48.5% and good median OS of 10.1 to 12.5 months.[10,11]

Because S-1 and GS have shown promising activity in PC, the present randomized phase III study (GEST [Gemcitabine and S-1 Trial] study) was designed to evaluate whether S-1 alone is noninferior to gemcitabine and whether GS is superior to gemcitabine alone for locally advanced and metastatic PC with respect to OS.

PATIENTS AND METHODS

Study Design

This randomized phase III study, sponsored by Taiho Pharmaceutical in Japan and TTY Biopharm in Taiwan, was conducted as a postmarketing study in Japan and as a registration study in Taiwan and was in compliance with the Declaration of Helsinki. Data were collected by a contract research organization contracted by the sponsors and were analyzed by a bio-statistician (Y.O.). An independent data and safety monitoring committee reviewed efficacy and safety data. The study was approved by the ethics committee or institutional review board of each participating center.

Patients

All patients provided written informed consent. Enrollment criteria were locally advanced or metastatic PC, histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events), an Eastern Cooperative Oncology Group performance status score of 0 to 1, and adequate organ functions (see Appendix, online only).

Treatment

Random assignment was performed centrally with stratification by extent of disease (locally advanced disease *v* metastatic disease) and institution using the minimization method. Patients allocated to gemcitabine alone received gemcitabine at a dose of 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Patients allocated to S-1 alone received S-1 orally twice daily at a dose according to the body-surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle. Patients allocated to GS received gemcitabine at a dose of 1,000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose according to the BSA (< 1.25 m^2, 60 mg/d; ≥ 1.25 to < 1.5 m^2, 80 mg/d; ≥ 1.5 m^2, 100 mg/d) on days 1 through 14 of a 21-day cycle. The dose levels of S-1 used in the GS group were based on the results of a previous phase II study of GS, in which 1,000 mg/m^2 of gemcitabine was combined with 120 mg/d, 100 mg/d, and 80 mg/d of S-1. In that study, the rate of treatment withdrawal due to adverse events was 41% (22 of 54 patients), the rate of grade 3 or worse neutropenia was 80%, and the dose was reduced in 56% of the patients (30 of 54 patients).[11] Consequently, 20 mg/d lower doses of S-1 than those used in the S-1 monotherapy group were used in the GS group in the present study.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see Appendix).

Assessments

Physical examinations, CBCs, and biochemistry tests were usually checked at 2-week intervals in the S-1 group and at each time of administration of gemcitabine both in the gemcitabine group and in the GS group. All adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. Computed tomography or magnetic resonance imaging was performed every 6 weeks until disease progression, and response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12] Quality of life was assessed using the EuroQol 5 Dimension questionnaire[13] at baseline and 6, 12, 24, 48, and 72 weeks after the study treatment had begun.

Statistical Analysis

The primary end point was OS, defined as time from date of random assignment to date of death from any cause. Secondary end points were progression-free survival (PFS), objective response rate, safety, and quality of life. PFS was counted from the date of random assignment to the date of death without progression or of progression as confirmed by the investigator's assessment. The median OS was assumed to be 7.5 months in the gemcitabine group, 8.0 months in the S-1 group, and 10.5 months in the GS group. To maintain a one-sided significance level of .025 for the entire study while testing two hypotheses (ie, noninferiority and superiority), the one-sided significance

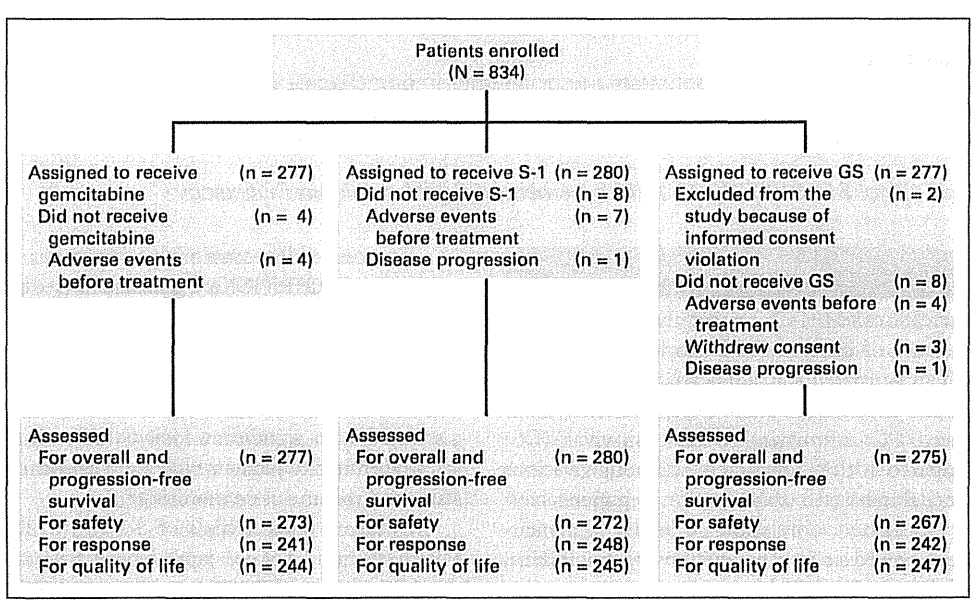

Fig 1. CONSORT diagram. GS, gemcitabine plus S-1.

level for each comparison was set at .0125. The statistical considerations are detailed in the Appendix.

The superiority of GS was evaluated by the stratified log-rank test. To assess the noninferiority of S-1, we used the Cox proportional hazards model to calculate two-sided, 97.5% CIs of the hazard ratio (HR). The noninferiority margin of S-1 was set at 1.33; that is, the null hypothesis was that the median OS with S-1 would be approximately 2 months shorter than with gemcitabine. We decided this setting was justified considering the convenience of S-1 and because there are few effective drugs for the disease. Furthermore, to interpret the obtained data, the Bayesian analysis of the log HR on the basis of the noninformative prior distribution was preplanned. Posterior probability with log HR within a stricter threshold (log 1.15) was also calculated.[14]

In each assigned group, the time-to-event distribution was estimated with the Kaplan-Meier method. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[15] In addition, the Greenwood formula[16] was used to calculate the 95% CI for survival rates. In subgroup analyses, interaction tests were performed to assess the homogeneity of the effect of treatment on OS.

The primary end point was analyzed for the full analysis set. All *P* value evaluations were two-tailed. Data analyses were done with SAS, version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patients

Between July 2007 and October 2009, a total of 834 patients were enrolled from 75 institutions in Japan and Taiwan (768 in Japan and 66 in Taiwan). Two patients in the GS group were excluded from the study because enrollment was conducted before obtaining written informed consent. The remaining 832 patients were included in the full analysis set and used to calculate OS and PFS (Fig 1). The three treatment groups were well balanced with respect to demographic and baseline characteristics (Table 1).

Study Treatment

The median duration of treatment was 2.6 months in the gemcitabine group, 2.6 months in the S-1 group, and 4.3 months in the GS group. The main reasons for treatment discontinuation were either disease progression (202 patients [72.9%] in the gemcitabine group,

Table 1. Demographics and Baseline Characteristics of Patients (full-analysis set population)

Characteristic	Gemcitabine (n = 277)		S-1 (n = 280)		GS (n = 275)		Total (N = 832)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	170	61.4	170	60.7	158	57.5	498	59.9
Female	107	38.6	110	39.3	117	42.5	334	40.1
Age, years								
< 65	134	48.4	145	51.8	137	49.8	416	50.0
≥ 65	143	51.6	135	48.2	138	50.2	416	50.0
ECOG PS								
0	181	65.3	178	63.6	172	62.5	531	63.8
1	96	34.7	102	36.4	103	37.5	301	36.2
Extent of disease								
Locally advanced	66	23.8	68	24.3	68	24.7	202	24.3
Metastatic	211	76.2	212	75.7	207	75.3	630	75.7
Type of tumor								
Adenocarcinoma	272	98.2	276	98.6	272	98.9	820	98.6
Adenosquamous carcinoma	5	1.8	4	1.4	3	1.1	12	1.4
Pancreas excision								
No	254	91.7	264	94.3	248	90.2	766	92.1
Yes	23	8.3	16	5.7	27	9.8	66	7.9
Tumor location*								
Head	122	44.0	110	39.3	116	42.2	348	41.8
Body	88	31.8	124	44.3	102	37.1	314	37.7
Tail	68	24.5	55	19.6	66	24.0	189	22.7
Biliary drainage								
No	202	72.9	217	77.5	209	76.0	628	75.5
Yes	75	27.1	63	22.5	66	24.0	204	24.5
CEA, ng/mL								
Median	5.7		5.6		5.9		5.7	
IQR	3.0-20.1		2.5-18.4		2.5-20.7		2.6-19.5	
CA19-9, U/mL								
Median	1,044		726		441		712	
IQR	52-5,002		64-5,000		45-5,090		55-5,002	
CRP, mg/dL								
Median	0.40		0.50		0.40		0.43	
IQR	0.11-1.38		0.18-1.57		0.15-1.60		0.15-1.57	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; GS, gemcitabine plus S-1; IQR, interquartile range.
*Including patients with tumors involving multiple sites.

215 [76.8%] in the S-1 group, and 162 [58.9%] in the GS group) or adverse events (40 patients [14.4%] in the gemcitabine group, 38 [13.6%] in the S-1 group, and 76 [27.6%] in the GS group). The median relative dose-intensity was 83.0% in the gemcitabine group, 96.1% in the S-1 group, and 83.3% for gemcitabine and 87.4% for S-1 in the GS group.

Survival

The median duration of follow-up for surviving patients was 18.4 months (range, 0.3 to 36.9 months) as of July 31, 2010. The analysis of OS was based on 710 deaths (85.3%) among the 832 patients. The median OS was 8.8 months (95% CI, 8.0 to 9.7) in the gemcitabine group, 9.7 months (95% CI, 7.6 to 10.8) in the S-1 group, and 10.1 months (95% CI, 9.0 to 11.2) in the GS group (Fig 2A). OS rates at 12 and 24 months were respectively 35.4% and 9.2% in the gemcitabine group, 38.7% and 12.7% in the S-1 group, and 40.7% and 14.5% in the GS group. The noninferiority of S-1 to gemcitabine with respect to OS was demonstrated (HR, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority). The Bayesian posterior probability that the HR of S-1 relative to gemcitabine would be less than 1.15 was calculated to be 98% on the basis of the noninformative prior distribution. However, GS failed to improve OS at a statistically significant level as compared with gemcitabine (HR, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$).

The analysis of PFS was based on 793 events (95.3%) among the 832 patients. The median PFS was 4.1 months (95% CI, 3.0 to 4.4) in the gemcitabine group, 3.8 months (95% CI, 2.9 to 4.2) in the S-1 group, and 5.7 months (95% CI, 5.4 to 6.7) in the GS group (Fig 2B). PFS rates at 6 and 12 months were respectively 29.8% and 9.1% in the gemcitabine group, 26.9% and 7.2% in the S-1 group, and 47.9% and 20.3% in the GS group. S-1 was shown to be noninferior to gemcitabine with respect to PFS (HR, 1.09; 97.5% CI, 0.90 to 1.33; $P = .02$ for noninferiority), and GS significantly improved PFS compared with gemcitabine (HR, 0.66; 97.5% CI, 0.54 to 0.81; $P < .001$).

Subgroup analyses of survival according to pretreatment characteristics showed no significant interaction between S-1 and gemcitabine in any subgroup (Fig 3A). However, GS showed a favorable HR compared with gemcitabine in the subsets of patients with locally advanced disease or patients with a performance status of 1 (Fig 3B).

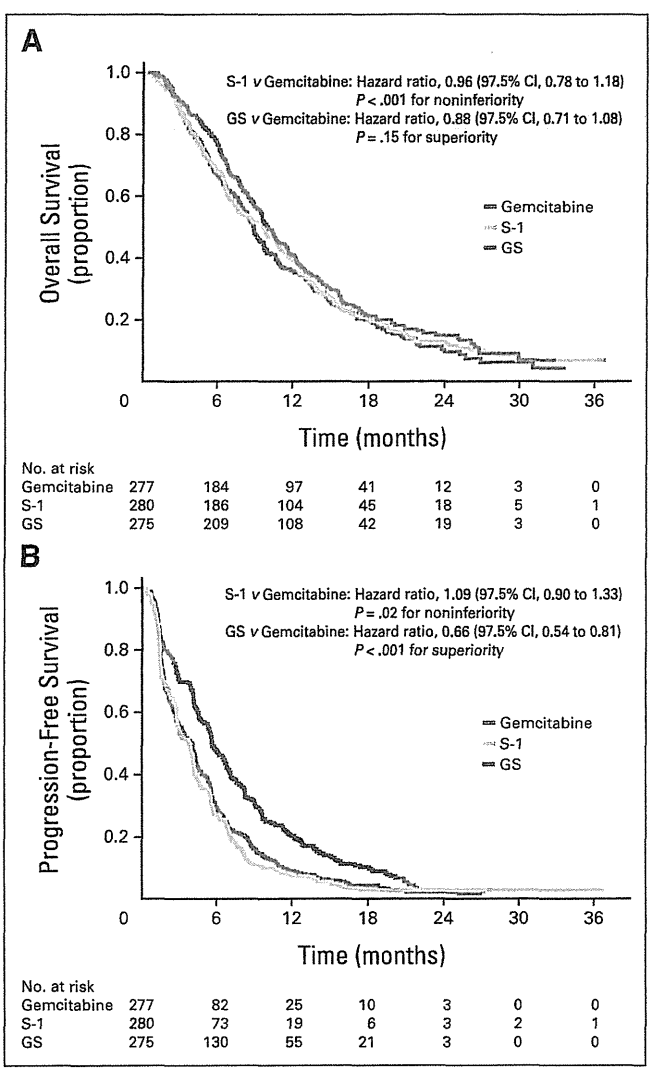

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival according to treatment group. GS, gemcitabine plus S-1.

Response to Therapy

The objective response rate was 13.3% (95% CI, 9.3 to 18.2) in the gemcitabine group, 21.0% (95% CI, 16.1 to 26.6) in the S-1 group, and 29.3% (95% CI, 23.7 to 35.5) in the GS group (Table 2). The objective response rate was significantly higher in the S-1 group ($P = .02$) and in the GS group ($P < .001$) than in the gemcitabine group.

Second-Line Chemotherapy

Second-line chemotherapy was performed in 184 patients (66.4%) in the gemcitabine group, 185 (66.1%) in the S-1 group, and 172 (62.5%) in the GS group. In the gemcitabine group, 140 patients (50.5%) received S-1 alone or S-1–based regimens, and in the S-1 group 162 (57.9%) received gemcitabine alone or gemcitabine-based regimens as second-line chemotherapy. The most common second-line regimens in the GS group were gemcitabine alone (61 patients), GS (53 patients), S-1 alone (24 patients), irinotecan (six patients), and fluorouracil/leucovorin plus oxaliplatin (four patients). In Japan and Taiwan, the use of treatments such as erlotinib, oxaliplatin, and irinotecan for PC was not approved at the time of this study; hence gemcitabine, S-1, or both were used in most patients as second-line chemotherapy.

Adverse Events and Quality-Adjusted Life-Years

The major grade 3 or worse adverse events are listed in Table 3. Patients in the gemcitabine group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, elevated AST levels, and elevated ALT levels as compared with patients in the S-1 group. However, the incidence of grade 3 or worse diarrhea was higher in the S-1 group than in the gemcitabine group. Patients in the GS group had significantly higher incidences of grade 3 or worse leukopenia, neutropenia, thrombocytopenia, rash, diarrhea, vomiting, and stomatitis than patients in the gemcitabine group.

There were three deaths considered possibly related to the protocol treatment (interstitial lung disease, sepsis, and acute hepatitis B) in the gemcitabine group, one in the S-1 group (unknown cause), and

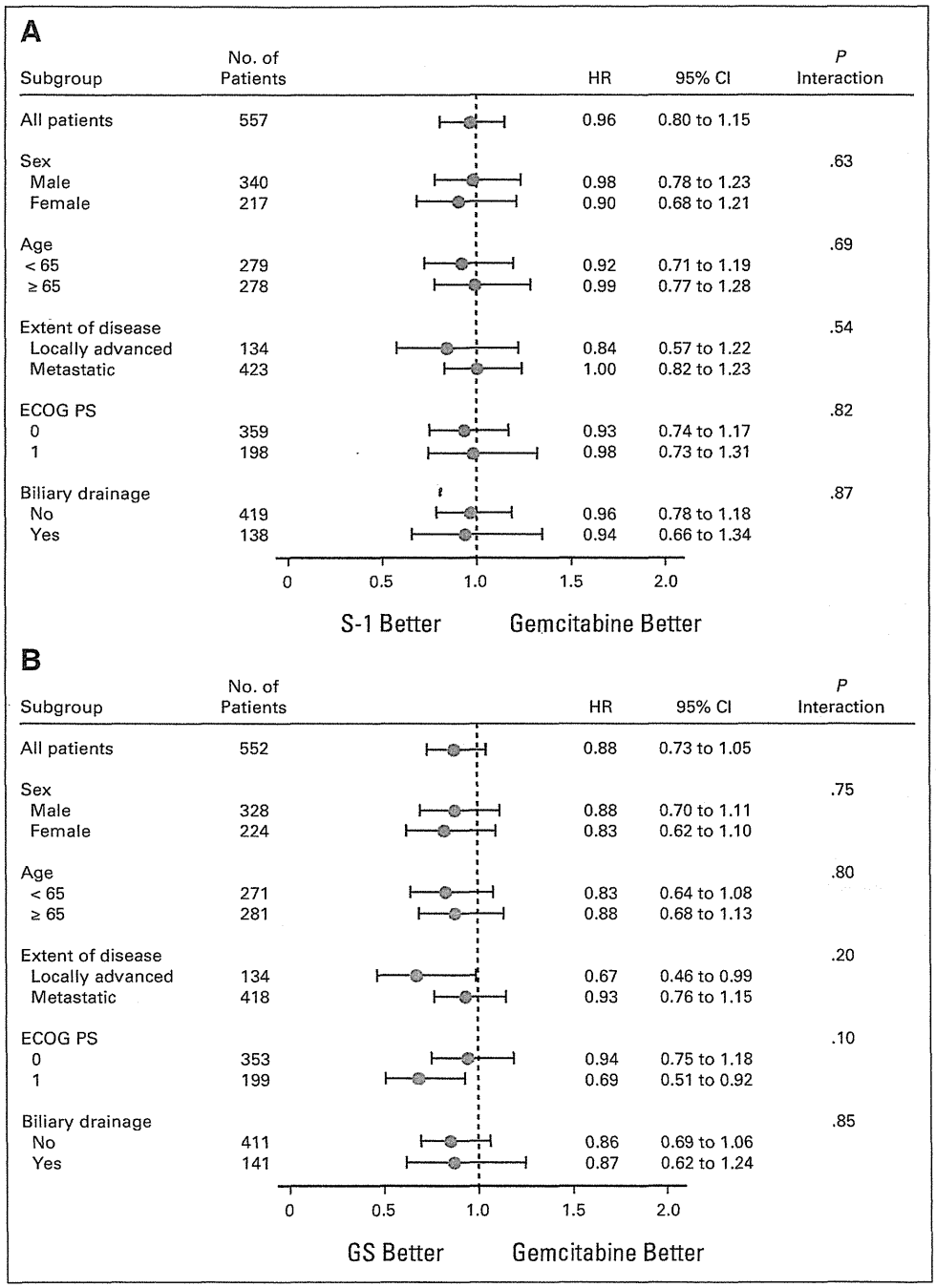

Fig 3. Forest plots of treatment effects on overall survival in subgroup analyses. Forest plots show effects on overall survival of patients in each subgroup. (A) S-1; (B) gemcitabine plus S-1 (GS). Each blue circle shows the treatment response. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

four in the GS group (unknown cause associated with myelosuppression, cerebral infarction, cerebrovascular disorder, and interstitial lung disease). The results of quality-adjusted life-years (QALYs) are in the Appendix and the details of quality-of-life assessments will be reported elsewhere.

DISCUSSION

The overall and PFS curves in the S-1 group were nearly identical to those in the gemcitabine group, confirming the noninferiority of S-1 to gemcitabine in terms of OS and PFS (Fig 2A, 2B). Toxicity profiles of these two drugs differed slightly: gemcitabine tended to show hematologic toxicity, whereas S-1 tended to show GI toxicity. However, both S-1 and gemcitabine were generally well tolerated. Furthermore, the results of QALY evaluation demonstrated that S-1 and gemcitabine were equivalent. Hence our results suggest that S-1 can be used as first-line therapy as a convenient oral alternative for locally advanced and metastatic PC. To the best of our knowledge, this is the first phase III study to demonstrate the noninferiority of a single anticancer agent to gemcitabine alone for locally advanced and metastatic PC.

Table 2. Objective Response Rates (patients with measurable lesions)

Variable	Gemcitabine (n = 241) No.	Gemcitabine (n = 241) %	S-1 (n = 248) No.	S-1 (n = 248) %	GS (n = 242) No.	GS (n = 242) %	*P* (χ^2 test) Gemcitabine *v* S-1	*P* (χ^2 test) Gemcitabine *v* GS
Response								
Complete response	1	0.4	0	0	2	0.8		
Partial response	31	12.9	52	21.0	69	28.5		
Stable disease	119	49.4	105	42.3	102	42.1		
Progressive disease	75	31.1	69	27.8	37	15.3		
Objective response rate*	32	13.3	52	21.0	71	29.3	.02	< .001
95% CI	9.3 to 18.2		16.1 to 26.6		23.7 to 35.5			
Disease control rate†	151	62.7	157	63.3	173	71.5	.88	.04
95% CI	56.2 to 68.8		57.0 to 69.3		65.4 to 77.1			

Abbreviation: GS, gemcitabine plus S-1.
*The objective response rate was defined as the proportion of patients who had a complete response or partial response.
†The disease control rate was defined as the proportion of patients who had a complete response, partial response, or stable disease.

At the time of planning this study, the participants of nearly all phase III trials included both patients with locally advanced as well as those with metastatic PC. However, because locally advanced and metastatic diseases are two clinical entities, it is recently recommended that patients with locally advanced disease should be studied separately from those with metastatic disease.[17] Although this study included locally advanced disease, subgroup analysis of extent of disease showed no significant interaction between S-1 and gemcitabine (Fig 3A). Moreover, the OS curve in the S-1 group was still similar to those in the gemcitabine group in both locally advanced and metastatic disease (Fig 4A, 4B). Regarding pathologic diagnosis, our study included adenosquamous carcinoma, although its percentage was very low (1.4% of whole population). When the data were reanalyzed after excluding patients with adenosquamous carcinoma, the results for OS for gemcitabine versus S-1 was unchanged (HR, 0.96; 95% CI, 0.81 to 1.15). The selection of one treatment over the other will depend primarily on patient preference, clinical factors, or drug costs, as biomarkers indicating effective use of S-1 or gemcitabine do not exist at this time.

Regarding GS, the OS did not differ significantly from gemcitabine, although the PFS was significantly longer in the GS group. Second-line chemotherapy mainly with S-1 in the gemcitabine group may be one reason for this discrepancy. The median OS in the gemcitabine group was 8.8 months, which is longer than those previously reported for gemcitabine in other phase III studies for locally advanced and metastatic PC.[2,3,18-24] Although the efficacy of second-line

Table 3. Grade 3 or Worse Adverse Events (safety population)

Event	Gemcitabine (n = 273) No.	Gemcitabine (n = 273) %	S-1 (n = 272) No.	S-1 (n = 272) %	GS (n = 267) No.	GS (n = 267) %	*P* (Fisher's exact test) Gemcitabine *v* S-1	*P* (Fisher's exact test) Gemcitabine *v* GS
Hematologic								
Leukocytes	51	18.7	10	3.7	101	37.8	< .001	< .001
Neutrophils	112	41.0	24	8.8	166	62.2	< .001	< .001
Platelets	30	11.0	4	1.5	46	17.2	< .001	.05
Hemoglobin	39	14.3	26	9.6	46	17.2	.11	.41
Nonhematologic								
ALT	41	15.0	16	5.9	29	10.9	< .001	.16
AST	41	15.0	21	7.7	32	12.0	.01	.32
Bilirubin	26	9.5	39	14.3	23	8.6	.09	.77
Fatigue	10	3.7	18	6.6	13	4.9	.13	.53
Rash	2	0.7	2	0.7	11	4.1	1.00	.01
Anorexia	20	7.3	31	11.4	25	9.4	.11	.44
Diarrhea	3	1.1	15	5.5	12	4.5	.004	.02
Mucositis/stomatitis	0	0.0	2	0.7	6	2.2	.25	.01
Nausea	5	1.8	5	1.8	12	4.5	1.00	.09
Vomiting	2	0.7	4	1.5	12	4.5	.45	.006
Febrile neutropenia	1	0.4	1	0.4	5	1.9	1.00	.12
Infection with normal ANC	6	2.2	7	2.6	6	2.2	.79	1.00
Pneumonitis	5	1.8	0	0.0	2	0.7	.06	.45

NOTE. Grades of adverse events were defined according to the Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviations: ANC, absolute neutrophil count; GS, gemcitabine plus S-1.

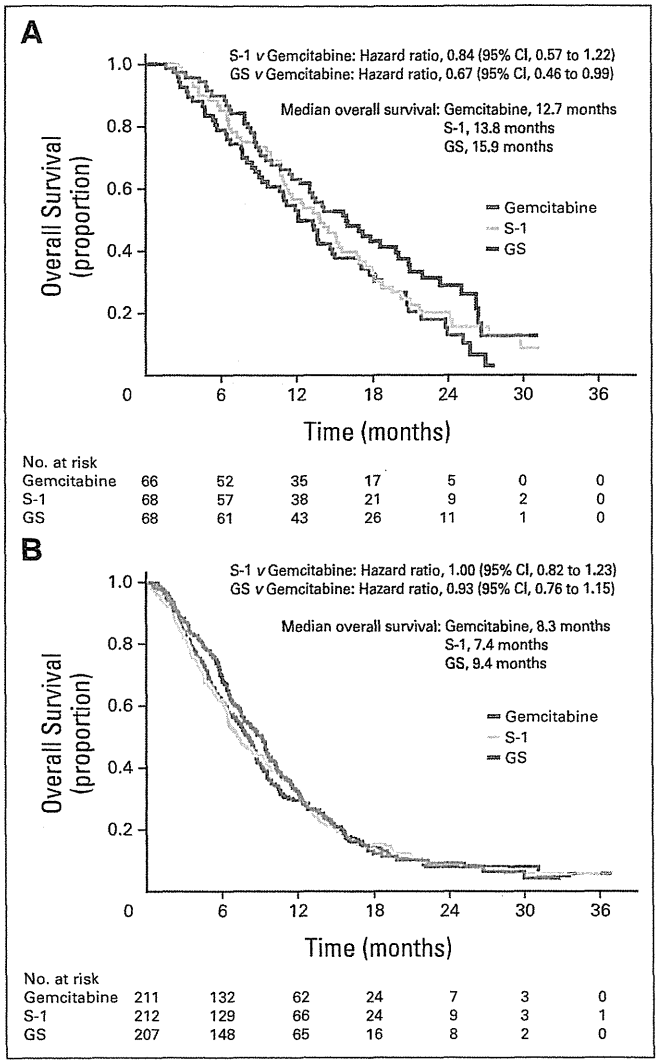

Fig 4. Kaplan-Meier estimates of overall survival in (A) locally advanced disease and (B) metastatic disease. GS, gemcitabine plus S-1.

therapy was not analyzed in this study, a phase II study of second-line S-1 in patients with gemcitabine-refractory PC showed a 15% response rate and 58% disease control rate.[25] Compared with the GS group, which had no promising second-line therapy, the use of S-1 as second-line therapy in the gemcitabine group might have contributed to prolonged survival.

The lack of a significant difference in OS between gemcitabine and GS suggests that gemcitabine and S-1 could be used sequentially rather than concurrently. However, the GS group showed a high response rate and favorable PFS, with a better HR of 0.66 compared with other gemcitabine-based combination regimens in other phase III studies (HR = 0.75 to 1.07).[3,18,20,22,24] Furthermore, the GS group showed a favorable HR for OS in patients with locally advanced disease or patients with a performance status of 1 in the subgroup analyses. Therefore, it is speculated that there may be room to select GS therapy, depending on the profile of the patients and further investigations.

Regarding oral fluoropyrimidines other than S-1, capecitabine has been studied in patients with PC, mainly in the West. In two phase III studies, a combination of gemcitabine plus capecitabine did not significantly prolong survival as compared with gemcitabine alone.[19,20] The results of a meta-analysis of these phase III studies, however, demonstrated that survival was significantly prolonged by combined treatment, with an HR of 0.86,[20] which is similar to the HR for GS in the present study (0.88).

One limitation of our study is that it is uncertain whether our results can be simply extrapolated to Western patients because pharmacokinetics and pharmacodynamics of S-1 between Westerners and East Asians may be different.[26,27] Although S-1 is available for PC only in Japan at the moment, if S-1 is used in Western patients, its effectiveness should be monitored and the dose should be carefully adjusted accordingly. Another potential limitation is that the protocol-specified noninferiority margin of 1.33 may be large. However, the result of point estimate of the HR of S-1 was 0.96 and actual upper limit of the 97.5% CI was 1.18, which was sufficiently lower than the prespecified margin of 1.33. Furthermore, Bayesian posterior probability with log HR within a stricter threshold (log 1.15) was 98%.

Given that most gemcitabine-based combination regimens have not been shown to be significantly superior to gemcitabine alone and that FOLFIRINOX has demonstrated overwhelming superiority to gemcitabine in a phase III study, reporting an HR of 0.57,[4] the development of gemcitabine-free combination regimens for first-line treatment seems to be warranted. However, because FOLFIRINOX requires the placement of a central venous access port for continuous intravenous infusion of fluorouracil, it can be expected that S-1, an oral fluoropyrimidine, will replace the continuous infusion of fluorouracil in the future.

In conclusion, this study has verified the noninferiority of S-1 to gemcitabine, thereby suggesting that S-1 can be used as first-line therapy for locally advanced and metastatic PC. Because S-1 was confirmed to be a key treatment for PC, S-1–based regimens are expected to be developed in the future to improve the management of this formidable disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

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Details of Adequate Organ Functions in Enrollment Criteria and Main Exclusion Criteria

Adequate organ functions were defined as follows: leukocyte count $\geq$ 3,500/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, hemoglobin level $\geq$ 9.0 g/dL, serum creatinine level $\leq$ 1.2 mg/dL, creatinine clearance $\geq$ 50 mL/min, serum AST and ALT levels $\leq$ 150 U/L, and serum total bilirubin level $\leq$ 2.0 mg/dL or $\leq$ 3.0 mg/dL if biliary drainage was performed.

Main exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; and serious complications such as heart failure, peptic ulcer bleeding, or poorly controlled diabetes. Pancreatic cancers other than adenocarcinoma or adenosquamous carcinoma (eg, anaplastic carcinoma) were excluded from the study.

Dosage Adjustment Guideline for Toxicities

All treatment cycles were repeated until disease progression, unacceptable toxicity, or patient refusal. If patients had a leukocyte count of less than 2,000/μL, a neutrophil count of less than 1,000/μL, a platelet count of less than 70×10^3/μL, or grade 3 or worse rash, the administration of anticancer agents was postponed. S-1 was temporarily halted both in S-1 and in GS groups if patients had a creatinine level of 1.5 mg/dL or higher or grade 2 or worse diarrhea or stomatitis. Treatment was discontinued if these events did not resolve within 4 weeks after treatment suspension. In patients who experienced febrile neutropenia, grade 4 leukopenia, neutropenia, or thrombocytopenia or grade 3 or worse rash, the dose of gemcitabine was reduced by 200 mg/m^2. In patients with febrile neutropenia; grade 4

leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

Gemcitabine in Patients With Intraductal Papillary Mucinous Neoplasm With an Associated Invasive Carcinoma of the Pancreas

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Objectives: The standard chemotherapy for invasive ductal carcinoma of the pancreas (IDC) is gemcitabine; however, the efficacy of gemcitabine in invasive intraductal papillary mucinous neoplasm with an associated invasive carcinoma of the pancreas (IPMN-IC) is still unknown.

Methods: Because it is difficult to distinguish between IPMN-IC and IDC based only on radiological findings in advanced unresectable cases, recurrent cases after surgical resection were analyzed to identify the efficacy of gemcitabine monotherapy for IPMN-IC.

Results: Between 1992 and 2010, 128 patients with IPMN-IC and 548 patients with IDC underwent pancreatic resection at the National Cancer Center Hospital. Twelve patients with IPMN-IC and 73 patients with IDC had recurred after surgery and subsequently underwent gemcitabine at the standard dosage. The disease-control rates were comparable between the IPMN-IC and IDC patients (58.3% vs 59.4%). The median progression-free survival was 2.8 and 4.1 months in the IPMN-IC and IDC patients, respectively ($P = 0.46$). Also, no statistically significant difference in the median survival times was observed between the 2 groups (9.3 vs 8.8 months, respectively; $P = 0.09$).

Conclusions: Among patients who had IPMN-IC and IDC with recurrent disease after resection, there was no significant difference in treatment outcomes after gemcitabine.

Key Words: chemotherapy, pancreatic cancer, IPMN, invasive ductal carcinoma of the pancreas, intraductal papillary mucinous carcinoma, IPMC

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Intraductal papillary mucinous neoplasm of the pancreas (IPMN) was first reported in Japan. The patients were described as having a dilated pancreatic duct with mucus hypersecretion, and a dilated orifice of ampulla.[1] The true incidence of IPMNs is unknown because they are usually asymptomatic and small; however, IPMNs have a pronounced malignant potential. The 10-year actuarial risk of developing invasive cancer was reported as being 29% in patients with highly probable or histologically proven IPMNs.[2] Moreover, there is a report that around 40% of patients have invasive malignancy at the time of diagnosis.[3] IPMNs with a component of invasive carcinoma led to the designation "IPMN with an associated invasive carcinoma (IPMN-IC)."[4] Although there are several reports of surgically resected IPMN cases, clinical outcomes and sensitivity to chemotherapy in patients with unresectable or recurrent IPMN-IC are still unknown. The aim of the present study was to identify the efficacy of chemotherapy for IPMN-IC. The chemotherapeutic regimen was limited to gemcitabine monotherapy, which is one of the standard regimens for invasive ductal carcinoma of the pancreas (IDC), and the treatment outcome was compared between IPMN-IC and IDC as reference. Because it is difficult to distinguish between IPMN-IC and IDC based only on radiological findings in advanced unresectable cases, we limited the target population of our study to recurrent cases of IPMN-IC and IDC patients whose definitive diagnosis was confirmed by pathological findings of the resected specimen.

MATERIALS AND METHODS

Patients

We reviewed the records of patients treated at the National Cancer Center Hospital between August 1992 and March 2010. One hundred twenty-eight consecutive patients with IPMN and 548 consecutive patients with IDC of the pancreas underwent pancreatic resection. In our hospital, patients were followed up for at least 5 years. The clinical data for patients who experienced a recurrence before July 2010 were then retrieved, and the treatments after recurrence were surveyed. Recurrences after surgery were diagnosed using computed tomography or magnetic resonance imaging. All patients provided written informed consent for chemotherapy before the initiation of treatment. The institutional review board of our center approved this retrospective study.

Classifications of IPMN

All the surgical specimens of the target population had been examined pathologically and a diagnosis of IPMN or IDC had been confirmed. The classification of IPMN was based on the World Health Organization classification[4] and International Consensus Guideline.[5] IPMNs were classified into 3 macroscopic types, namely, main duct type, branch duct type, and mixed type.[5] We diagnosed the macroscopic types by macroscopic examinations of resected samples. Furthermore, IPMNs were classified into the following 4 subtypes using histopathological and immunohistochemical findings: gastric type, intestinal type, pancreatobiliary type, and oncocytic type. The morphological types were diagnosed according to criteria described previously that were based on the predominant architectural and cell differentiation pattern.[4,6–8] We performed immunohistochemistry using antibodies against mucin 1 (MUC1) (Ma552), mucin 2 (MUC2) (Ccp58), mucin 5AC (MUC5AC) (CLH2), mucin 6 (MUC6) (CLH5), and CDX-2 (AMT28). These were all

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purchased from Novocastra Laboratories Ltd (Newcastle-upon-Tyne, UK). IPMNs were further categorized into 2 types with regard to invasion, namely, noninvasive IPMN (IPMN with low-grade, intermediate-grade, or high-grade dysplasia) or IPMN-IC.[4] Noninvasive IPMN was restricted to the pancreatic duct wall. IPMN-IC had a definite invasion into the pancreatic parenchyma. With respect to the staging of the invasion, the T1 category in the American Joint Committee on Cancer/TNM (invasive carcinoma of <2 cm) was divided into the following 3 subcategories: T1a, T1b, and T1c.[5,9] The T1a subcategory was formerly referred to as "minimally invasive" and was defined as invasive carcinoma measuring less than or equal to 5 mm.[5,10–14]

Statistical Analysis

Distributions of variables between 2 groups were compared using the χ^2 test for categorical data and the Mann-Whitney U test for continuous data. Objective response rate was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.0.[15] Survival times were estimated using the Kaplan-Meier method, and compared using the log-rank test. Recurrence-free survival was defined as the interval between surgical resection and recurrence. Progression-free survival was calculated from the date of the initiation of gemcitabine monotherapy until documented disease progression, or death due to any cause (whichever occurred first). Overall survival was defined as the time from initiation of gemcitabine monotherapy to the date of death or the last follow-up. Differences with values of $P < 0.05$ were considered as being statistically significant.

TABLE 1. Demographic and Tumor Characteristics

	IPMN-IC	IDC	
	n = 12	n = 73	*P*
At the time of pancreatic resection			
Age, median (range), y	70 (53–79)	63 (39–80)	0.04
Sex, n (%)			
Male	6 (50)	45 (62)	0.45
Female	6 (50)	28 (38)	
AJCC stage, n (%)			
I	3 (25)	0	0.01
IIa	2 (17)	9 (12)	
IIb	5 (41)	57(78)	
III/IV	2 (17)	7 (10)	
CEA median (range), ng/mL	9.6 (1.2–434.0)	5.9 (0.7–213.0)	0.48
CA19-9, median (range), U/mL	48 (2–6510)	596 (1–25270)	0.08
At the time of recurrence			
Age, median (range), y	73 (54–80)	64 (40–81)	0.03
Recurrent free survival, mo	14.4	7.5	0.04
Recurrent site, n (%)			
Liver	6 (50)	20 (40)	0.93
Local	2 (17)	21 (29)	
Lung	1 (8)	11 (15)	
Lymph	3 (25)	9 (12)	
Others	0	11 (15)	

AJCC indicates American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

TABLE 2. Summary of Efficacy Measures

	IPMN-IC	IDC	
	n = 12	n = 73	*P*
Level of response, n			
Complete	0	0	
Partial	0	2	
Stable disease	7	42	
Response rate, %	0	2.7	0.56
Disease-control rate, %	58.3	60.3	0.90
Progression-free survival, median, mo	2.8	4.1	0.46
Overall survival, median, mo	9.3	8.8	0.09

Statistical analysis was performed using R version 2.12.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We selected 12 patients with IPMN-IC and 73 patients with IDC who received gemcitabine monotherapy after recurrence and were followed up in our center. The clinical findings involving recurrent IPMN and IDC patients are shown in Table 1. All of the recurrent IPMN patients were classified using pathological findings from resected specimens as having IPMN-IC, including 3 patients with T1a carcinoma. The median recurrence-free survival time after surgery for the IPMN-IC patients was longer than that for the IDC patients (14.4 vs 7.5 months, respectively; $P = 0.04$). Patients with IPMN-IC were diagnosed at an earlier stage at the time of resection.

In all patients, gemcitabine monotherapy was initiated at the standard dosage after recurrence. The antitumor effects and prognosis are summarized in Table 2. The disease-control rates were comparable between the IPMN-IC and IDC patients (58.3% vs 60.3%, respectively). The median progression-free survival was 2.8 and 4.1 months in the IPMN-IC and IDC patients, respectively ($P = 0.46$). At the time of disease progression, second-line chemotherapy was administered in 58% of the IPMN-IC patients and in 33% of the IDC patients ($P = 0.09$). No statistically significant difference in overall survival times was observed between the IPMN-IC and IDC groups (median, 9.3 vs 8.8 months, respectively; $P = 0.09$) (Fig. 1).

Among the IPMN-IC patients, the macroscopic classifications of the IPMN at the time of resection were main duct

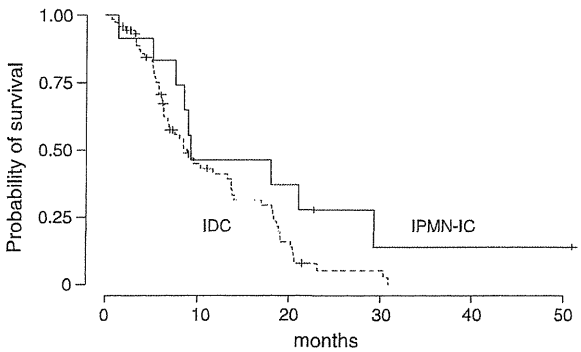

FIGURE 1. Kaplan-Meier analysis of overall survival after initiation of gemcitabine. The median survival time was 9.3 and 8.8 months in the IPMN-IC and IDC patients, respectively ($P = 0.09$).

TABLE 3. Classifications of IPMN at the Time of Resection

	Macroscopic Type		
	Main Duct	Branch Duct	Mixed
	n = 6	n = 2	n = 4
Histopathological subtype, n (%)			
Pancreatobiliary	5 (83)	1 (50)	2 (50)
Intestinal	1 (17)	1 (50)	1 (25)
Oncocytic	0	0	1 (25)
Invasion, n (%)			
T1a (minimally)	1 (17)	1 (50)	1 (25)
Colloid	1 (17)	0	0
Tubular	4 (66)	1 (50)	3 (75)

type in 6 patients, mixed type in 4, and branch duct type in 2. Regarding the subtypes of the IPMN, 8 were the pancreatobiliary type, 3 were the intestinal type, and 1 was the oncocytic type (Table 3). In comparing the main duct and mixed type with the branch duct type, the median survival times from initiation of gemcitabine were 18.0 and 8.1 months, respectively ($P = 0.08$). Between the pancreatobiliary type and others, the median survival times from initiation of gemcitabine were 21.1 and 8.5 months, respectively ($P = 0.09$). Survival times after initiation of gemcitabine in 3 patients with T1a carcinoma were 1.5, 7.6, and 18.0 months. Survival times after pancreatic resection in these patients were 15.3, 61.7, and 37.0 months, respectively. The subtype of all of the patients with minimally invasive carcinoma was the intestinal type.

DISCUSSION

Since the first report was described in Japan,[1] IPMNs of the pancreas have been discovered with increasing frequency because of the improvement in diagnostic imaging techniques. IPMNs express a latent or overt malignant potential. Although resected IPMN-IC has a favorable prognosis as compared with IDC,[16–21] the prognosis for advanced IPMN-IC is reported to be as poor as advanced IDC.[18] In clinical practice, one of the standard regimens of first-line chemotherapy for advanced pancreatic cancer remains gemcitabine monotherapy. To our knowledge, there have been no reports on the efficacy of chemotherapy for advanced or recurrent IPMN-IC. Our study evaluated the efficacy of gemcitabine for IPMN-IC, which is a standard regimen for IDC, and showed that IPMN-IC and IDC exhibited no significant difference in treatment outcomes from the start of gemcitabine monotherapy for the recurrent disease.

In advanced pancreatic cancer, the proportion of IPMN-IC has been reported to be less than 5%.[22–24] The carcinogenic pathway involved in the conversion of noninvasive IPMN to IPMN-IC is often compared with that involved in the conversion of pancreatic intraepithelial neoplasia (PanIN) to the invasive ductal carcinoma sequence.[25] Some disparities between IPMN and PanIN exist. In contrast to PanIN and ductal adenocarcinoma, *DPC4* loss or mutation in *p16* is uncommon in IPMNs.[26–32] Thus, the carcinogenesis of IPMNs may differ from those of PanINs and conventional ductal adenocarcinomas. Our study did not show a significant difference in clinical behavior such as chemosensitivities or outcomes between IPMN-IC and IDC. Because the results of our study were based on a small number of patients, further studies are needed to evaluate whether the difference in carcinogenesis may affect treatment effects.

The main duct type IPMNs including the mixed type show a more aggressive clinical course than the branch duct type IPMNs. The prevalence of invasive carcinoma at diagnosis has been reported to be higher in patients with main duct type than in patients with branch duct type.[5] Moreover, patients with main duct type and mixed type have a poorer prognosis than patients with branch type in surgical resected cases.[33] IPMN-IC is typically divided into of the following 2 histologic types: tubular type (conventional ductal adenocarcinoma) and colloid type (mucinous adenocarcinoma).[8] With respect to the histopathological classification of IPMNs, invasive cancer arising from the pancreatobiliary type is usually the tubular type carcinoma that is morphologically indistinguishable from IDC and has a poorer prognosis than other types.[33] The subgroup analysis of IPMN-IC in our study showed that the patients with the main duct type or the pancreatobiliary type had favorable prognoses, albeit that it was not statistically significant. Although the reason why these results seemed paradoxical when compared with previous reports could not be adequately explained, it may be partially due to an insufficient sample size. Additionally, the pancreatobiliary type is reported to be a less common disease entity than other types.[8,33] However, the most common subtype of IPMNs in our study was the pancreatobiliary type. This discrepancy may be due to the bias of patient selection in our study because we limited the target population to patients with recurrent status; this in itself indicated the clinically aggressive nature of the cancer. Regarding the type of invasion, the recurrence rate and prognosis for T1a carcinoma (formerly "minimally invasive carcinoma") is better than that for invasive carcinoma as reported previously.[10,11,14] However, our study showed that once recurrence had occurred, prognosis was poor even for T1a carcinoma. One patient with T1a carcinoma had an extremely aggressive clinical course with a survival time after initiation of gemcitabine that was only 1.5 months, and a survival time after pancreatic resection was 15.3 months.

In conclusion, there was no significant difference in the treatment outcomes after gemcitabine monotherapy between IPMN-IC and IDC in patients with recurrent disease after surgical resection. When we take into account the lack of other promising treatment regimens, our results do not deny the appropriateness of gemcitabine use in clinical practice of IPMN-IC. The number of patients in this study was limited and further studies are needed to define the role of gemcitabine in this disease.

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DISEASES OF THE ESOPHAGUS

Case report

Multimodal endoscopic treatment for delayed severe esophageal stricture caused by incomplete stent removal

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SUMMARY. **The usefulness of a covered self-expandable metallic stent for benign esophageal stricture and perforation was well established. In case of benign disease, early stent removal was recommended within 6–8 weeks after placement. A case with severe esophageal stricture caused by incomplete stent removal 7 years after stent placement for spontaneous esophageal rupture was reported. Residual stent fragments could be removed by step-by-step multimodal endoscopic treatment, producing satisfactory luminal diameter of the esophagus. In particular, stent trimming with argon plasma coagulation was safe and effective strategy. The endoscopic stent removal is minimally invasive and should be attempted before surgical intervention; however, it is most important to ensure early stent removal before tissue ingrowth or overgrowth can develop.**

INTRODUCTION

Although rare, spontaneous rupture of the esophagus, or Boerhaave's syndrome, is a potentially fatal condition. Surgical treatment has long been considered the 'gold standard' response. However, if the diagnosis is delayed, a surgical procedure can cause morbidity and mortality.[1,2] Over the past few years, various invasive endoscopic treatment options have emerged. It has recently been reported that the temporary placement of a covered self-expandable metallic stent is an effective treatment for sealing a benign esophageal rupture and perforation.[3–9] However, stent-related complications, such as stent migration and tissue ingrowth or overgrowth, have been reported.[4,5,8–10] Reactive benign tissue ingrowth or overgrowth can cause stricture, especially when stents remain in place for long periods.[4,8–10] Endoscopic stent removal in cases of severe stent embedding may cause esophageal perforation,[4,9,11] and the embedded stent must be removed by force after it is cut into pieces during a surgical intervention. Incomplete stent removal can lead to further esophageal stricture. We report a patient with severe esophageal stricture induced by residual stent fragments after surgical stent removal, and its multimodal endoscopic treatment.

CASE REPORT

A 56-year-old man suffered spontaneous rupture of his esophagus. We placed a covered self-expandable metallic stent over the fistula just above the esophagogastric junction. After this treatment, the patient's condition improved dramatically. We attempted to remove the stent endoscopically 3 months after its placement, but it was too firmly fixed to the esophageal wall to allow it to be extracted through the patient's mouth (Fig. 1). The stent was removed surgically, piece by piece, via the gastric wall after it had been cut into pieces with scissors, but some stent fragments remained in the esophagus (Fig. 2). Our colleagues have reported the clinical course of the acute stages of this case.[12] During 7 years of observation since the laparotomy, the patient showed worsening dysphagia because granulation tissue developed around the residual stent fragments (Fig. 3). The protruding granulation tissue was removed using a

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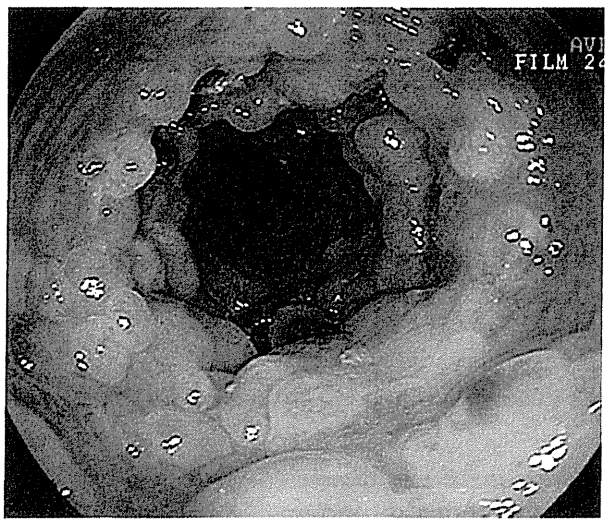

Fig. 1 The stent was firmly fixed to the esophageal wall because of tissue ingrowth.

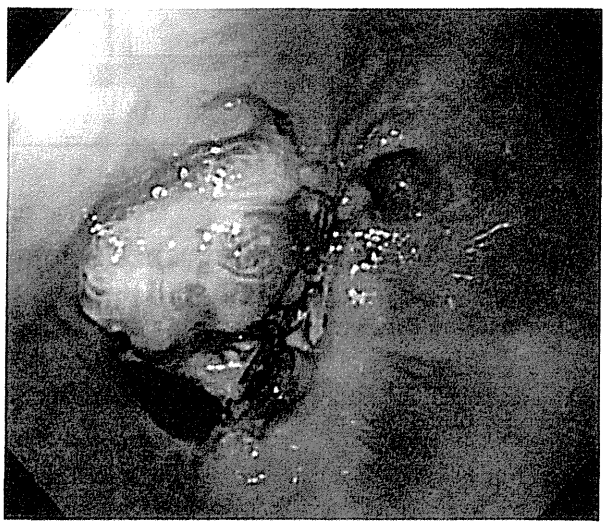

Fig. 3 Step 1: Esophageal lumen was occupied by protruding granulation tissue around the residual stent fragments. Large polypoid lesion was removed using a snare.

snare (step 1), but the patient's symptoms remained unchanged. One and a half years later after step 1, an exposed stent fragment was trimmed using argon plasma coagulation (APC) (Figs 4,5; step 2). The power setting was 30–40 W, and the argon gas flow was set at a rate of 1.0–1.2 L/min using an argon plasma electrosurgical generator (VIO 300D/APC2, Erbe, Tübingen, Germany). Three days later after step 2, several stent fragments were removed with grasping forceps via the patient's mouth after balloon dilatation of the esophagus (Fig. 6; step 3). After almost all the stent fragments had been removed, 5 months later after step 3, the residual granulation tissue formed 'bridges' across the esophageal lumen (Fig. 7), which were severed with a diathermic knife and a snare, producing a satisfactory luminal diameter of the esophagus (Fig. 8; step 4). The patient is currently asymptomatic 3 years later after step 4 without further treatment.

DISCUSSION

The rate of successful clinical sealing after temporary endoscopic stent placement for a benign esophageal rupture and perforation has been reported to be about 80%, with low morbidity and mortality.[6–9] The major reported complications of endoscopic stent placement are stent migration and tissue ingrowth or overgrowth.[4,5,8–10,13] Fibrosis and the proliferation of granulation tissue around the stent result from the

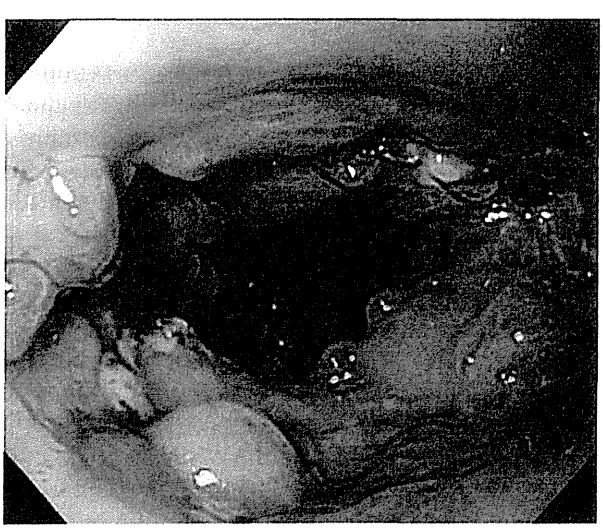

Fig. 2 Some stent fragments remained in the esophageal wall after removing the stent surgically, piece by piece via the gastric wall.

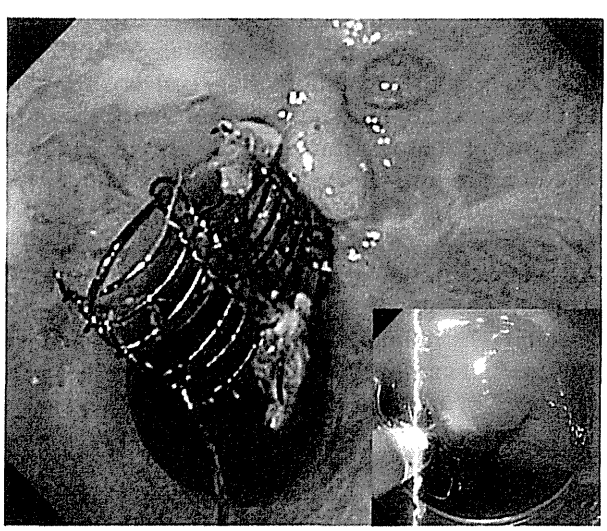

Fig. 4 Stent fragment exposed to the esophageal lumen after the removal of the protruding granulation tissue. We tried to trim the stent fragment with argon plasma coagulation (inset).

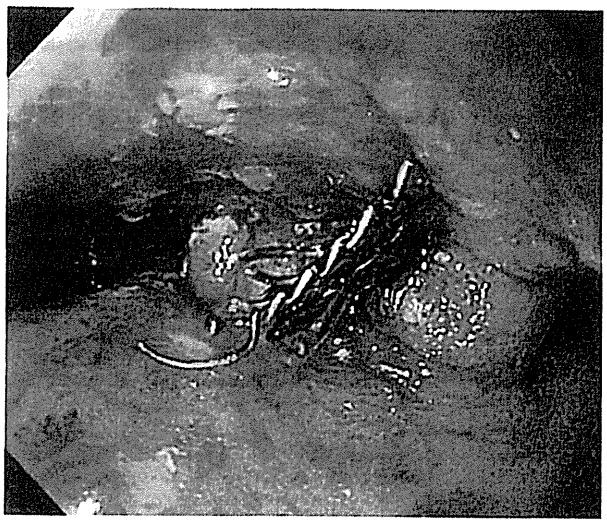

Fig. 5 Step 2: Part of a stent fragment exposed to the esophageal lumen could be trimmed with argon plasma coagulation (one and a half years later after step 1).

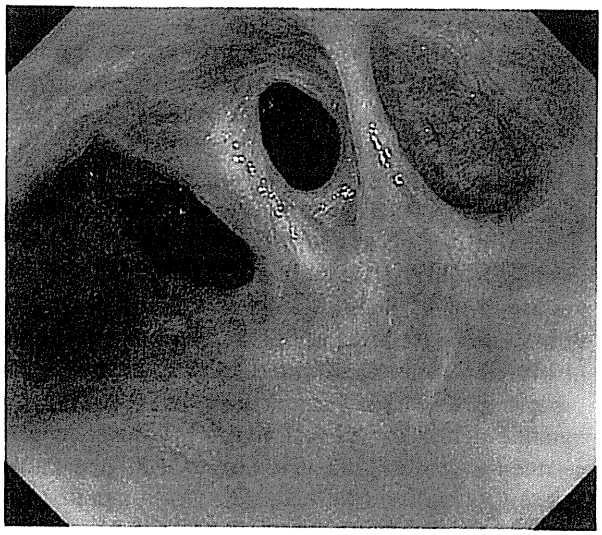

Fig. 7 Residual granulation tissue forming several 'bridges' across the esophageal lumen.

foreign body reaction to the stent,[14] and tissue ingrowth or overgrowth may occur in 5–8% of patients.[8,9] The stent can become firmly embedded in the esophageal wall, especially with long-term placement, and its removal may entail complications such as bleeding, tearing off the mucosa, and perforation.[4,9,11,13] In some of these patients, subsequent surgical intervention may be required to forcibly remove the embedded stent in a piecemeal fashion. However, it is sometimes difficult to ensure that all the fragments of the stent are removed completely.[3,4,12,13] As a result, secondary severe stricture caused by residual stent fragments can develop in the long term.

Over the past few years, three different type of a stent such as a partially (PSEMS) and a fully covered self-expandable metallic stent (FSEMS), and a self-expandable plastic stent (SEPS) has been able to be selected for a benign esophageal rupture and perforation. van Boeckel *et al.* have reported that stent migration occurred most frequently with FSEMS followed by SEPS and PSEMS, while tissue ingrowth or overgrowth was only seen with PSEMS.[9] However, the same group reported in their review that stent migration occurred more often with FSEMS and SEPS, whereas there was no significant difference in tissue ingrowth or overgrowth between them.[8] Moreover, like our case, Jaganmohan and Raju reported their cases in which even FSEMS can be complicated by tissue ingrowth.[15] Even though tissue ingrowth or overgrowth tends to be higher with PSEMS

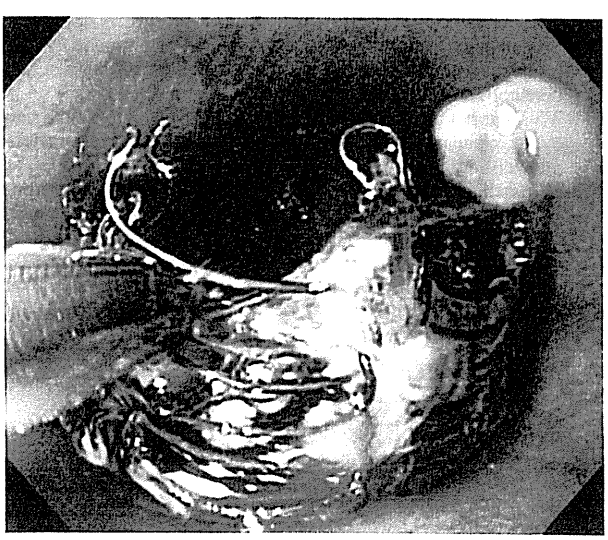

Fig. 6 Step 3: Some stent fragments were removed with grasping forceps after balloon dilatation of the esophagus (3 days later after step 2).

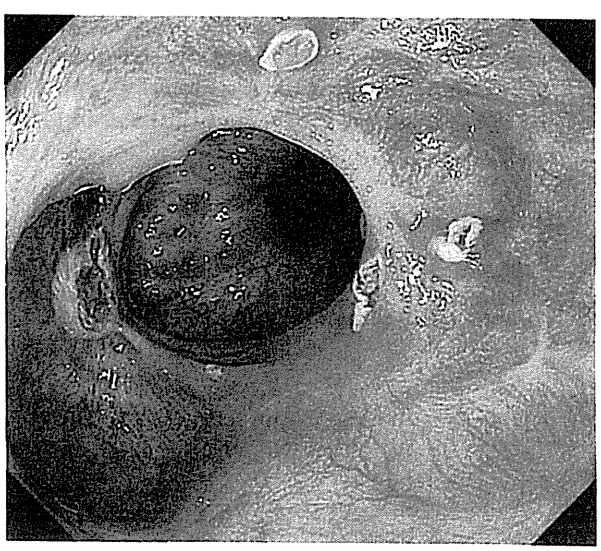

Fig. 8 Step 4: Granulation 'bridges' were severed with a diathermic knife and a snare, producing a satisfactory luminal diameter of the esophagus (5 months later after step 3).

compared with the other two, such complication may occur regardless of the stent type. As efficacy between them was not found to be significantly different, stent choice should depend on the expected risks of complications with a particular stent type.[8,9]

In our patient, step-by-step multimodal endoscopic treatment made it possible to remove the stent fragments through the patient's mouth and to relieve the stricture without surgical reintervention. Recently, the use of APC to trim a metallic stent in the biliary tract, duodenum, colon, or rectum to relieve an obstruction has been reported.[16–18] However, few reports are available about the use of APC to trim a metallic stent in the esophagus.[15,17] We have demonstrated for the first time that residual fragments after the surgical removal of an esophageal metallic stent can be trimmed safely using APC. The endoscopic removal of the stent, including its fragmentation with APC, is minimally invasive and should be attempted before surgical intervention.

However, it is most important to ensure early stent removal because tissue ingrowth or overgrowth is related to the duration of stenting in the esophagus.[8,9,13] van Heel *et al.* reported that the stent had been in place significantly longer in patients who underwent a complicated stent removal than in those with an uncomplicated primary stent removal.[13] Moreover, it has recently been recommended to remove embedded metallic stent that FSEMS of the same diameter should be placed inside embedded stent.[8,9,19] This stent-in-stent technique causes necrosis of the hyperplastic tissue ingrowth or overgrowth. Hirdes *et al.* reported that both these stents could be removed uneventfully after a period of 10–14 days.[19]

In conclusion, thanks to the technological advances and in the hands of skillful endoscopists, endoscopic removal of esophageal stents can avoid surgery. However, we emphasize that temporary stents used for benign disease should be removed before tissue ingrowth or overgrowth can develop (within 6–8 weeks of placement) regardless of the stent type.[9,13]

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