Association Between Time to Stent Dysfunction and the Anti-Tumour Effect of Systemic Chemotherapy Following Stent Placement in Patients With Pancreaticobiliary Cancers and Malignant Gastric Outlet Obstruction: A Retrospective Cohort Study

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Association between time to stent dysfunction and the anti-tumour effect of systemic chemotherapy following stent placement in patients with pancreaticobiliary cancers and malignant gastric outlet obstruction: A retrospective cohort study

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Abstract

Background: Malignant gastric outlet obstruction (MGOO) occasionally occurs due to pancreaticobiliary cancer. Endoscopic duodenal stenting (DS) is a common treatment for MGOO. However, it has been reported that DS does not have sufficient patency time for it to be used in patients who have a potentially increased lifespan. Nowadays, systemic chemotherapy for pancreaticobiliary cancer has developed, and its anti-tumour effect would make time to stent dysfunction longer.

Therefore, we retrospectively evaluated the association between objective response to systemic chemotherapy followed by DS and time to stent dysfunction in patients with advanced pancreaticobiliary cancer.

Methods: This retrospective study included 109 patients with advanced pancreaticobiliary cancer who received systemic chemotherapy after DS. Patients who showed complete or partial response were defined as responders. The rest were defined as non-responders. Time to stent dysfunction was compared between responders and non-responders using the landmark analysis, at 2 months after DS. Death without recurrence of MGOO was considered as a censored case for time to stent dysfunction.

Results: Combination and monotherapy regimens were adopted for 41 and 68 patients, respectively. Median progression-free survival and overall survival were 3.2 months (95% confidence interval [CI], 2.4-4.0) and 6.0 months (95% CI, 4.6-7.3). Objective response was

observed in 21 patients (19.3%). Patients who received combination regimens had longer progression-free survival and higher response rates than those who received monotherapy regimens; progression-free survival was 5.1 months (95% CI, 3.1-7.0) and 2.6 months (95% CI, 1.6-3.5) with a p-value of <0.001, and response rates were 39.0% and 7.4% with a p-value <0.001, respectively. Median time to stent dysfunction was 12.5 months (95% CI, 8.4-16.5) in the entire cohort. In 89 patients, responders had longer time to stent dysfunction than non-responders: 17.4 months (95% CI, 17.3-17.5) and 7.1 months (95% CI, 1.6-12.5), respectively, with a p-value of 0.031.

Conclusions: Longer time to stent dysfunction is expected when systemic chemotherapy following DS suppresses tumour progression; DS is slated to be a standard treatment for MGGO even in patients with pancreaticobiliary cancer and a long lifespan.

Keywords: duodenal stenting, systemic chemotherapy, cancer, stent dysfunction, response

BACKGROUND

Pancreatic cancer is the third leading cause of cancer-related death in the United States; death due to this disease accounted for approximately 43,000 cases in 2017.[1] It was the fourth leading cause of cancer death in Japan in 2018.[2] Biliary tract cancer includes the malignant cancer originating from the extrahepatic and hilar bile ducts, gallbladder, and ampulla of Vater. It is a relatively rare cancer in the United States or Europe; however, it is more common in East

Asian countries, accounting for 18,000 cases in Japan. As the disease progresses, the primary tumour grow up; malignant gastric outlet obstruction (MGOO) due to tumour invasion through the layers of the gastroduodenal wall occurs in approximately 10-20% of patients with pancreaticobiliary cancer.[3-5] Gastric outlet obstruction is a crucial issue for patients with these cancers, because it induces nausea, vomiting, and anorexia, which can result in life-threatening comorbidities.

Gastrojejunostomy (GJ) has been widely used as a palliative treatment option for MGOO; in the early 1990s, duodenal stenting (DS) was first developed and reported as an alternative procedure to GJ.[6] According to the reviews of some clinical trials, DS is especially recommended for patients with MGOO who had a life expectancy of less than 3 months, since the patency of DS is approximately 3 months and additional interventions are often required.[7-9]

Advanced pancreaticobiliary cancer has a poor prognosis, even in patients who received systemic chemotherapies after resolving MGOO, since systemic chemotherapies (such as gemcitabine (GEM) monotherapy) had little efficacy in prolonging patient survival and a low response rate.[10, 11] Patients with advanced pancreaticobiliary cancer were candidates for DS, even if they could receive subsequent chemotherapy after resolving MGOO. We evaluated the clinical effectiveness and safety of DS for patients with pancreatic cancer[12] and concluded that DS was an effective treatment for patients with advanced pancreatic cancer

and MGOO, in terms of its safety and smooth performance of subsequent chemotherapies.

In recent years, systemic chemotherapies have been developed for advanced pancreaticobiliary cancer, such as FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin)[13] and GEM plus nab-paclitaxel[14] for pancreatic cancer, and GEM plus cisplatin[15] and GEM plus S-1 for biliary tract cancer.[16] Response rate for these regimens has been reported as 30-60%; overall survival was 10-11 months.[17] Based on these data, patients who were candidates for these regimens will be suitable for GJ rather than for DS, as the treatment option for MGOO; however, DS can be another option if chemotherapy can prolong the patency of DS. Therefore, in this study, we aimed to assess the association between time to stent dysfunction (TTSD) for DS and efficacy of systemic chemotherapy.

METHODS

Patients

This was a retrospective cohort study. We reviewed the medical records of 317 consecutive patients with advanced pancreaticobiliary cancer who underwent DS for MGOO at our institution between July 2010 and December 2019. Patients enrolled in this study were also provided the opportunity to opt out of having any information published.

Duodenal stenting

99 We considered patients as candidates for endoscopic DS if they met the following criteria as
100 described in our previous report[12]: 1) unresectable or recurrent disease that could not be
101 cured with surgical resection; 2) histologically or cytologically proven pancreaticobiliary
102 cancer; and 3) MGOO due to a stricture in the stomach or duodenum that was confirmed
103 through radiological or endoscopic findings. Duodenal stent placement was contraindicated for
104 patients who met the following conditions: 1) small bowel strictures or functional disorder
105 induced by peritoneal dissemination; 2) stent placement risk factors due to haemorrhagic status
106 or cardiopulmonary problems; 3) life expectancy of less than two weeks. We used several types
107 of stents, such as the WallFlex or WallFlex Duodenal Soft (Boston Scientific Corporation,
108 Marlborough, MA, USA) (22 mm with a proximal flare of 24 mm in diameter); Niti-S D
109 pyloric/duodenal, and Niti-S COMVI™ Pyloric duodenal (Taewoong Medical Co., Ltd., Seoul,
110 Korea) (22 mm in diameter without proximal flares); HANAROSTENT® Naturfit™ Duo (22
111 mm in diameter without proximal flares) (Boston Scientific Corporation, Marlborough, MA,
112 USA). Stent lengths vary from 60 to 120 mm; we selected the stent according to the stricture
113 length. The Niti-S COMVI™ was only used for patients at risk of tumour haemorrhage because
114 it is a covered stent. Uncovered stents were used at the physician's discretion. Stent placement
115 was performed under sedation; the stricture was mainly identified endoscopically. In cases
116 where the stricture was located at the distal end of the horizontal portion of the duodenum, we
117 performed fluoroscopic duodenography using a contrast medium (Gastrografin Oral Enema,

Bayer HealthCare Pharmaceuticals, Leverkusen, Germany) to identify the stricture. A 0.035-inch guidewire (Hydra Jagwire, Boston Scientific Corporation) was inserted through the stricture, and the duodenal stent was positioned across it, under fluoroscopic guidance. Stent length was chosen according to the stricture length and the position of the pylorus/ampulla of Vater. Finally, the stent was deployed, and its patency was confirmed by injection of the contrast medium. Types of DSs used with each patient depended on the physician's discretion and their availability. After stent placement, patients could resume consuming liquids on day 1, soft foods on day 2, and solid foods on day 3, as long as no symptoms of MGOO exacerbation were observed. In cases of MGOO recurrence, a second/third duodenal stent was placed using the stent-in-stent technique.

Systemic chemotherapy after duodenal stenting

We considered applying systemic chemotherapy after duodenal stenting for patients who met the following criteria: 1) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; 2) achievement of full oral intake; 3) adequate liver and kidney functions; 4) preserved bone marrow function: neutrophil count $>1500/\mu\text{L}$; platelet count $>100,000/\mu\text{L}$; and 5) a life expectancy of at least 3 months. We chose the chemotherapy regimens according to each patient's consent and conditions, as follows: e.g., patients who had ECOG PS of 0-1 and were aged <75 years were introduced to combination chemotherapeutic regimens, such as modified

FOLFIRINOX[18] or GEM plus nab-paclitaxel for pancreatic cancer, or GEM plus cisplatin or GEM plus S-1 for biliary tract cancer. Patients who were ineligible for these combination regimens (but eligible for less toxic therapies) were introduced to monotherapy regimens, such as GEM alone or S-1 alone. We adopted these regimens not only as first-, but also as second- or third-line treatments. The initial dose of each agent was reduced at the physician's discretion. Chemotherapy continued until disease progression, intolerable adverse events, or patient refusal.

Clinical outcomes

Diagnosis of stent occlusion or migration was confirmed based on radiological and/or endoscopic findings and not on symptoms such as nausea or vomiting. TTSD was determined starting from the date of DS through the date of diagnosis of stent dysfunction. Tumour ingrowth and overgrowth, stent migration, and food impaction were considered as stent dysfunction-related events. Patients who died without stent dysfunction were treated as censored cases for the evaluation of TTSD. Additionally, we complementarily evaluated TTSD by considering the impossibility of oral intake due to disease progression. Overall survival and progression-free survival were determined starting on the date of initiation of systemic chemotherapy through the date of documented disease progression or any cause of death and the date of death due to any cause or the last follow-up, respectively. The best response during

chemotherapy was radiologically evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1.[19]

Statistical analysis

Results are expressed as median and were analysed using the SPSS Statistics 23 software (IBM SPSS, Inc., Chicago, IL, USA). Changes in the MGOO score[4] before and after duodenal stent placement were evaluated using the Wilcoxon signed-rank test. We calculated overall survival, progression-free survival, and TTSD using the Kaplan-Meier method; we used the log-rank test to compare these time-to-event parameters in two groups. Objective response to systemic chemotherapy was evaluated according to the new response evaluation criteria in solid tumours, version 1.1.[19] Patients were divided into the two groups according to the objective response to chemotherapy. Patients who showed complete or partial responses were defined as responders, and those who showed stable or progressive disease were defined as non-responders. We compared the TTSD of responders with that of non-responders by conducting a landmark analysis (landmark at 2 months after DS) to avoid guarantee-time bias and evaluate the association between TTSD and efficacy of systemic chemotherapy after DS.

RESULTS

Patient characteristics

Of 319 consecutive patients who had undergone DS, the study included 109 patients who received systemic chemotherapy after DS (Figure 1). Patient characteristics are shown in Table 1. Primary diseases were pancreatic adenocarcinoma, biliary tract cancer, and pancreatic neuroendocrine neoplasm in 92, 12, and 3 patients, respectively. Median age of the enrolled patients was 68 years (range: 31-81); 85 patients (77%) had metastatic cancer and 52 of them had peritoneal dissemination.

Duodenal stent placement

The duodenal stents used were WallFlex, Niti-S D type, HANAROSTENT® Naturfit™ Duo, Niti-S COMVI™, and WallFlex Soft in 46, 46, 10, 4, and 3 patients, respectively. Strictures were located on the oral side, above, and anal side of the papilla of Vater in 33, 26 and 50 patients, respectively. Among those, 6 patients with a MGOO score of 3 required DS: MGOO on the horizontal part of the duodenum was complicated with cholangitis in 3 patients; 2 patients had strictures in both the duodenal bulb and common bile duct; hence, DS was required before endoscopic retrograde biliary stenting. The MGOO score was better after DS compared to that before it, with a p-value <0.001. The median time required to tolerate food intake was just 1 day (range: 1-18 days).

Systemic chemotherapy

Median time from the date of stent placement through the date of initiation of chemotherapy was 12 (range: 1-60) days. Combination and monotherapy regimens were adopted for 41 and 68 patients, respectively. Median progression-free survival and overall survival were 3.2 months (95% CI, 2.4-4.0) and 6.0 months (95% CI, 4.6-7.3) (Figures 2a and 2b). Regarding the objective response, partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 21, 45, and 43 patients, respectively. Response and disease control rates were 19.2% and 60.6%, respectively. Patients who received combination regimens had longer progression-free survival and higher response rates than those who received monotherapy regimens; progression-free survival was 5.1 months (95% CI, 3.1-7.0) and 2.6 months (95% CI, 1.6-3.5) with a p-value of <0.001 (Figure 2c), and response rates were 39.0% and 7.4% with a p-value <0.001, respectively. In addition, 17 patients who received combination regimens as first-line treatments had a median progression-free survival of 8.6 months (95% CI, 1.5-15.6) (Supplement Figure 1) and a response rate of 58.8%.

Time to duodenal stent dysfunction

During the median observation time of 4.8 (range: 0.5–35.6) months, stent dysfunction was observed in 38 patients (35%) and impossibility of oral intake due to disease progression was observed in 53 (49%); the remaining 19 patients were censored at the time of analysis. The median TTSD was 12.5 months (95% CI, 8.4-16.5) (Figure 3a). When using a supplementary

definition of stent dysfunction, median TTSD was 5.0 months (95% CI, 4.3-5.7) in the entire cohort and 12.5 months (95% CI, 2.7-22.3) in patients who received combination regimens as the first-line treatment (Supplement Figure 2).

Landmark analysis at the 2-month landmark point revealed that TTSD was longer in responders (n = 21) than in non-responders (n = 68), [17.4 months (95% CI, 17.3-17.5) and 7.1 months (95% CI, 1.6-12.5) with a p-value of 0.031, respectively] (Figure 3b). There were differences in TTSD between responders and non-responders in patients who received combination regimen (Figure 3c) or a first-line treatment after DS (Figure 3d), with p-values of 0.043 and 0.024, respectively. Multivariable analysis showed that non-responders was a marginal poor prognostic factor for TTSD; hazard ratio was 2.5 (95% CI, 0.93-6.7), with a p-value of 0.070 (Table 2).

DISCUSSION

According to previous studies, DS is inferior to GJ in terms of TTSD, although DS is superior to GJ in terms of safety, rapid symptom relief, and shorter time required to resume food intake. Based on the results, treatment recommendations for pancreatic cancer by the National Comprehensive Cancer Network and Japanese Pancreas Society state that proper use of the two treatment options may depend on the patients' prognostic estimates.[20][21] These

recommendations do not state which is better for patients who will receive chemotherapy; their references date from 2000 to 2010, when the response rate of systemic chemotherapy was dismal. In recent decades, systemic chemotherapy for advanced pancreaticobiliary cancer has developed. Therefore, we evaluated the influence of chemotherapy on TTSD in patients who underwent DS and subsequent chemotherapy in 2010-2018. Our results showed that TTSD after DS was prolonged after chemotherapy through tumour shrinkage, especially when using a combination regimen. Therefore, DS could be a good treatment option, not only for patients with short life expectancy, but also for those who are eligible for a combination regimen and can expect an increased life expectancy. In other words, DS can be applied to all patients with unresectable pancreaticobiliary cancer as a standard treatment option for MGGO, along with advances in chemotherapy.

There are several reports on the effect of chemotherapy on TTSD of biliary stent; some studies have concluded that chemotherapy decreased TTSD by inducing bacterial colonisation in the bile ducts through its side effect of immunosuppression;[22] others have stated opposite conclusions, speculating that positive effect via tumour control would compensate for its negative effect in patients who received chemotherapy.[23] Regarding DS, the main causes of stent dysfunction are tumour growth and food impaction. Bacterial colonisation does not influence its patency. Therefore, we believe this might be a reason why chemotherapy has positive effects on TTSD of DS. Kim et al. have also reported that time to progression was an

independent protective factor against restenosis of DS in patients with gastric cancer.[24] When that report was published, the response rate and time to progression of chemotherapy for unresectable gastric cancer was around 30-40% and 5-7 months, respectively.[25, 26] These values were close to those of recent standard chemotherapy for advanced pancreaticobiliary cancer.[13-16] Patients who received combination regimens in our study had a median progression-free survival of 5.1 months and response rate of 39.0%. Therefore, we think this was another reason why our study could show the association between TTSD for DS and the effects of chemotherapy.

Overall survival was 4.6 months or longer in 95% of the patients included in our cohort. According to this review article,[7] surgical bypass is recommended for patients with a life expectancy of 3 months or longer; most patients had been eligible for surgical bypass rather than for DS. However, in this study, TTSD for DS was long enough that the patients survived without recurrent MGOO; median TTSD was 12.5 months in the primary definition of stent dysfunction and median time to impossibility of oral intake was 5.0 months. Furthermore, patients who received combination regimens as the first-line treatment could have 12.5 months of oral food intake. Based on the results, we believe that DS could be also recommended as a treatment option for MGOO for patients who are scheduled to receive intensive first-line chemotherapy for unresectable pancreaticobiliary cancer. Development of systemic chemotherapy for these diseases is awaited; DS will have longer TTSD in the future than

nowadays along with the improvement in response rate and progression-free survival in the future. Regarding safety, DS is considered a better option than surgical bypass, unless complications included stent dysfunction.[7, 9] Although we did not compare DS with surgical bypass in this study, we believe that DS is neither inferior to surgical bypass in terms of efficacy, nor superior in terms of safety.

The existing definition of stent dysfunction has affected the results, as the majority of patients could not eat orally due to disease progression; their stents were found to be patent, even in the final phase of the life. Regarding biliary stenting, the TOKYO criteria (2014) for transpapillary biliary stenting recommend patient death and complications other than recurrent biliary obstruction requiring stent removal be treated as censored cases at the time of death or stent removal, respectively.[27] According to the above-mentioned criteria, our primary definition of stent dysfunction was set as recurrent MGOO with stent thrombosis or migration. Primary data analysis showed that stent dysfunction was only observed in one third of patients. The small number of events will lower the statistical power to detect differences; hence, we conducted a supplementary analysis using disease progression as an event, to support the robustness of the primary analysis.

This study has some limitations. Its small number of patients and retrospective design are likely to cause several biases. Our study did not have a surgical bypass cohort; therefore, direct comparison between DS and surgical bypass was impossible. Indications for each

chemotherapy regimen depended on the physician's discretion. In addition, patients and regimens in this study formed a complex combination of several diseases and regimens.

CONCLUSIONS

Despite these limitations, we concluded that the anti-tumour effects of systemic chemotherapy improve TTSD of DS in pancreaticobiliary cancers; DS could be preferable not only for patients who have a life expectancy of less than 3 months, but also for those who are scheduled to receive systemic chemotherapy and are slated to have a longer life expectancy. Therefore, DS can be the standard treatment option for MGOO in unresectable pancreaticobiliary cancers.

List of Abbreviations

MGOO, malignant gastric outlet obstruction

DS, duodenal stenting

TTSD, time to stent dysfunction

ECOG PS, Eastern Cooperative Oncology Group performance status

308 **DECLARATIONS**

309 **Ethics approval and consent to participate**

310 All patients provided written informed consent for duodenal stent placement; all eligible
311 patients for subsequent chemotherapy also provided written informed consent. In addition, this
312 study was performed in accordance with the Declaration of Helsinki, and approved by the
313 Institutional Review Board of the Kanagawa Cancer Center in April 2020.

314

315 **Consent for publication**

316 **Not applicable**

317

318 **Availability of data and materials**

319 The datasets analysed during the current study are available from the corresponding author on
320 reasonable request.

321

322 **Competing Interests**

323 S.K received honoraria from Boston Scientific and Taiho Pharmaceutical. M.U. received
324 honoraria from MSD, Ono Pharmaceutical, Taiho Pharmaceutical, and Yakult Honsha Co., Ltd.
325 All other authors have no conflict of interest to declare.

326

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Authors' contributions

SK, SN, YS, KK, TF, HA, and ST analysed the patient data regarding the efficacy of duodenal stenting and systemic chemotherapy. SK, MU, and MM interpreted the data. SK was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figure Legends

427 Figure 1. CONSORT flow diagram of the study

428 Of 319 patients who received duodenal stent placement for malignant gastric outlet
 429 obstruction due to advanced pancreaticobiliary cancer, 109 received systemic chemotherapy
 430 followed by duodenal stent placement, and 89 had two months or longer to stent dysfunction.

431

432 Figure 2.

433 Kaplan-Meier curve of (a) overall survival and (b) progression-free survival

434 In the entire cohort, which consisted of 109 patients, median progression-free survival and
 435 overall survival rates after duodenal stent placement were 3.2 months (95% confidence interval,
 436 2.4-4.0) and 6.0 months (95% confidence interval, 4.6-7.3), respectively.

437 (c) Comparison of 41 patients who received combination regimen (solid line) and 68 patients
 438 who received a monotherapy regimen (dotted line), median progression-free survival rates
 439 were 5.1 months (95% confidence interval, 3.1-7.0) and 2.6 months (95% confidence interval,
 440 1.6-3.5) respectively, with a p-value of <0.001

441

442 Figure 3. Time to stent dysfunction

443 (a) Entire cohort

444 Median time to stent dysfunction was 12.5 months (95% confidence interval, 8.4-16.5);

445 (b) Comparison between patients who showed a response (solid line) and those who did not

(dotted line).

Median time from the 2-month landmark point to stent dysfunction was 17.4 months (95% confidence interval, 17.3-17.5) in patients who showed a response and 7.1 months (95% confidence interval, 1.6-12.5) in those who did not, with a p-value of 0.031;

(c) Comparison between responders and non-responders among patients who received combination regimen.

Median time from the 2-month landmark point to stent dysfunction was 17.4 months (95% confidence interval, 10.2-17.5) in responders and 5.0 months (95% confidence interval, 3.0-6.9) in non-responders, with a p-value of 0.043;

(d) Comparison between responders and non-responders among patients who received systemic chemotherapy after duodenal stent placement as the first-line chemotherapy.

Median time from the 2-month landmark point to stent dysfunction was 33.6 months (95% confidence interval, non-evaluable) in responders and 5.6 months (95% confidence interval, non-evaluable) in non-responders, with a p-value of 0.024.

Supplement Figure 1. Kaplan-Meier curves of progression-free survival in patients who received a combination regimen as the first- (solid line), second-, or third-line treatments (broken line) and those who received monotherapy as the first- (chained line), second-, or third-

465 line treatments (dotted line).

466 Median progression-free survival with 95% confidence interval was 5.8 months (0.2-11.5), 3.6
467 months (2.4-4.9), 1.1 months (0.2-2.0) and 2.8 months (0.9-4.6), respectively.

468

469 Supplement Figure 2. Kaplan-Meier curve of time to stent dysfunction when impossible oral
470 food intake was considered an event of stent dysfunction.

471 Median time to stent dysfunction was 5.0 months (95% CI, 4.3-5.7) in the entire cohort (solid
472 line) and 12.5 months (95% CI, 2.7-22.3) in patients who received combination regimens as
473 the first-line treatment (dotted line).

474

475 **TABLES**

476 Table 1. Baseline characteristics of patients at initiation of systemic chemotherapy following
 477 duodenal stent placement

Characteristics	
Age (years), median (median)	68.0 (31-81)
Sex, n (%)	
Male	54 (50)
Female	55 (50)
Primary disease, n (%)	
Pancreatic adenocarcinoma	90 (83)
Biliary tract adenocarcinoma	15 (14)
Pancreatic neuroendocrine tumour	4 (4)
Disease status, n (%)	
Locally advanced	24 (22)
Metastatic	85 (78)
ECOG performance status	
0	18 (17)
1	62 (57)
2	29 (27)
Position of bowel stricture, n (%)	
Oral side of the papilla of Vater	33 (30)
Above the papilla of Vater	26 (24)
Anal side of the papilla of Vater	50 (46)

Duodenal stent, n (%)	
WallFlex Duodenal	46 (42)
WallFlex Duodenal Soft	3 (3)
Niti-S D type	46 (42)
Niti-S COMVI™	4 (4)
HANAROSTENT® Naturfit™ Duo	10 (9)
Number of chemotherapy regimens prior to duodenal stenting, n (%)	
0	47 (43)
1	49 (45)
2-3	13 (12)
CRP (mg/dL), median (range)	
0.79 (0.05-12.9)	
Distribution, n (%)	
<1.0 mg/dL	60 (55)
≥1.0 mg/dL	49 (45)
Albumin (g/dL), median (range)	
3.3 (2.1-4.1)	
Distribution, n (%)	
<3.5 mg/dL	67 (62)
≥3.5 mg/dL	42 (39)
CA19-9 (U/mL), median (range)	
928.9 (0-408800.0)	
Distribution, n (%)	
<1,000 U/mL	55 (50)
≥1,000 U/mL	54 (50)

479 carbohydrate antigen 19-9

480

481 Table 2. Multivariate analysis of prognostic factor for time to stent dysfunction[†]

Factor	Hazard ratio	95% CI	p-value
Primary disease			
Pancreatic adenocarcinoma	1	N.E.	
Biliary tract cancers	0.29	0.06-1.40	0.12
Pancreatic neuroendocrine tumours	0.99	0.21-4.78	0.99
Disease status			
Locally advanced	1		
Metastatic	1.84	0.75-4.50	0.19
ECOG PS			
0-1	1		
2-3	1.47	0.46-4.74	0.52
Chemotherapy regimen			
Combination	1		
Mono-	1.38	0.57-3.37	0.48
Response to chemotherapy [§]			

Partial response	1		
Stable or progressive disease	2.49	0.93-6.67	0.070

482 † Cox proportional hazards regression model in patients who had a 2-month or longer time to

483 stent dysfunction

484 § According to the New response evaluation criteria in solid tumours, version 1.1

485 ¹ CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance

486 status; Combo, combination regimens such as FOLFIRINOX, gemcitabine plus nab-paclitaxel,

487 gemcitabine plus cisplatin and gemcitabine plus S-1; Mono, monotherapy such as gemcitabine

488 alone or S-1 alone

489

490

491

Figure 1

Figure 2

Figure 3

Figures

Figure 1

Figure 1

CONSORT flow diagram of the study Of 319 patients who received duodenal stent placement for malignant gastric outlet mobstruction due to advanced pancreaticobiliary cancer, 109 received systemic chemotherapy followed by duodenal stent placement, and 89 had two months or longer to stent dysfunction.

Figure 2

Figure 2

Kaplan-Meier curve of (a) overall survival and (b) progression-free survival In the entire cohort, which consisted of 109 patients, median progression-free survival and overall survival rates after duodenal stent placement were 3.2 months (95% confidence interval, 2.4-4.0) and 6.0 months (95% confidence interval, 4.6-7.3), respectively. (c) Comparison of 41 patients who received combination regimen (solid line) and 68 patients who received a monotherapy regimen (dotted line), median progression-free survival rates

were 5.1 months (95% confidence interval, 3.1-7.0) and 2.6 months (95% confidence interval, 1.6-3.5) respectively, with a p-value of <0.001

Figure 3

Figure 3

Time to stent dysfunction (a) Entire cohort Median time to stent dysfunction was 12.5 months (95% confidence interval, 8.4-16.5); (b) Comparison between patients who showed a response (solid line) and those who did not (dotted line). Median time from the 2-month landmark point to stent dysfunction was

17.4 months (95% confidence interval, 17.3-17.5) in patients who showed a response and 7.1 months (95% confidence interval, 1.6-12.5) in those who did not, with a p-value of 0.031; (c) Comparison between responders and non-responders among patients who received combination regimen. Median time from the 2-month landmark point to stent dysfunction was 17.4 months (95% confidence interval, 10.2-17.5) in responders and 5.0 months (95% confidence interval, 3.0-6.9) in non-responders, with a p-value of 0.043; (d) Comparison between responders and non-responders among patients who received systemic chemotherapy after duodenal stent placement as the first-line chemotherapy. Median time from the 2-month landmark point to stent dysfunction was 33.6 months (95% confidence interval, non-evaluable) in responders and 5.6 months (95% confidence interval, non-evaluable) in non-responders, with a p-value of 0.024.

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