Suggestion of added value by bevacizumab to chemotherapy in patients with unresectable or recurrent small bowel cancer

大嶋, 琴絵

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Kotoe Takayoshi[1,2], Hitoshi Kusaba[1], Masato Uenomachi[3], Kenji Mitsugi[3], Chinatsu Makiyama[4], Akitaka Makiyama[4], Keita Uchino[5], Tsuyoshi Shirakawa[6], Yoshihiro Shibata[7], Yudai Shinohara[2], Kyoko Inadomi[1], Kenji Tsuchihashi[1], Shuji Arita[8], Hiroshi Ariyama[1], Taito Esaki[2], Koichi Akashi[1], Eishi Baba[8]

1. Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
2. Department of Gastrointestinal and Medical Oncology, National Hospital Organization Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan
3. Department of Oncology, Hamanomachi Hospital, 3-3-1, Nagahama, Chuou-ku, Fukuoka 810-8539, Japan
4. Department of Hematology and Oncology, Japan Community Healthcare Organization Kyushu Hospital, 1-8-1, Kishinoura, Yahatanishi-ku, Kitakyushu 806-8501, Japan
5. Department of Medical Oncology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, 1-8-1, Jigyouhama, Chuou-ku, Fukuoka 810-0065, Japan
6. Department of Oncology, Miyazaki Prefectural Miyazaki Hospital, 5-30, Kita-takamatsucho, Miyazaki 880-8510, Japan
7. Department of Medical Oncology, Fukuoka Wajiro Hospital, 2-2-75, Wajirooka, Higashi-ku, Fukuoka 811-0213, Japan
8. Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Corresponding author: Eishi Baba, M.D., Ph.D.
Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University. 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
Phone +81-92-642-6921, Fax +81-92-642-6922
Email: e-baba@c-oncology.med.kyushu-u.ac.jp

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Abstract

Purpose: Standard therapy for advanced small bowel adenocarcinoma (SBA) has not yet been established. The present study assessed the efficacy and safety of chemotherapy (CT) in association with molecular targeting approaches for SBA.

Methods: The histories of 33 advanced SBA patients from six different institutions in Japan, who received CT from 2008 to 2016, were retrospectively examined for background, clinical course and outcome.

Results: Median patient age was 65 years (range 39-83). Primary tumor was located in the duodenum in 21 patients (67%), the ampulla of Vater in three patients (9%), the jejunum in seven patients (21%) and the ileum in one patient (3%). Histologically, well to moderately- and poorly-differentiated adenocarcinoma were identified in 20 (61%) and nine (27%) of patients, respectively. Thirteen patients received a single CT regimen, seven patients received two types of CT regimen, and 13 patients received three or more CT regimens. As first-line CT, modified FOLFOX6, capecitabine plus oxaliplatin, and S-1 plus cisplatin were employed in thirteen, one, and four patients, respectively. The response rate (RR) and median progression-free survival (PFS) were 25% and 6.0 months, respectively. Median overall survival (OS) was 13.0 months. Nine out of the 33 patients received bevacizumab-containing CT and three received cetuximab-containing CT. Median OS of bevacizumab-containing CT patients was 21.9 months. No unexpected serious adverse events were observed.

Conclusions: The analysis indicates that combination CT for advanced SBA is associated with modest efficacy and safety, and that bevacizumab-containing CT may contribute to favorable outcome in these patients.

Introduction

Malignant neoplasms of the small bowel are rare diseases. They account for less than 3% of neoplasms of the gastrointestinal tract, and consist of adenocarcinoma, lymphoma, carcinoid and sarcoma [1]. One third of small bowel neoplasms are adenocarcinomas (SBAs), with 56% of these originating in the duodenum [2]. SBA is relatively difficult to diagnose because of its anatomical location [1], and thus 35-40% of patients possess distant metastases at initial diagnosis [3,4]. Prognosis of SBA is poor, with a 5-year survival rate of 30% and a median overall survival (OS) of 19 months across all disease stages [5]. Five-year survival of patients with stage IV disease however, is reported to be as low as 3-4% [5].

While systemic chemotherapy (CT) is generally performed for SBA patients with unresectable or metastatic disease, a standard CT regimen has not yet been established and the CT regimens of advanced colorectal cancer (CRC) and gastric cancer (GC) are thus employed. These regimens, which include 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, and irinotecan, have been based on the results of phase II and retrospective studies, since no randomized, prospective clinical study for advanced SBA has so far been conducted [6-9]. A phase II study examining the combination of capecitabine and oxaliplatin (CAPOX) in 25 advanced SBA patients without prior CT, indicated a response rate (RR) of 52% and a median OS of 20.4 months [6]. A prospective phase II study involving a modified combination of fluorouracil, oxaliplatin, and leucovorin (mFOLFOX) administered to 33 SBA patients in China, demonstrated a RR of 48.5% and a median OS of 15.2 months [7]. The combination of fluorouracil, irinotecan, and leucovorin (FOLFIRI) was assessed in a retrospective study of SBA patients resistant to platinum-based CT, and revealed a median OS of 10.5 months, median progression-free survival (PFS) of 3.2 months and a RR of 20% [8]. Other retrospective studies have also suggested that fluorouracil, platinum and irinotecan may be effective for advanced SBA [9,10].

The clinical benefits of molecularly targeted agents, such as anti-VEGF (vascular endothelial growth factor) antibodies and anti-EGFR (epithelial growth factor receptor) antibodies for advanced CRC, and anti-HER2 (human epidermal growth factor receptor 2) antibody and anti-VEGFR (VEGF receptor) antibody for GC have been demonstrated [11-14]. However, the clinical impacts of a molecularly targeted agent for advanced SBA remain unclear, partly because the molecular characteristics of SBA have not been well described. A previous analysis identified *KRAS* (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) and *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) V600E gene mutations in 43% and

2.5% of SBA tumors, respectively, and HER2 protein overexpression in 3.2% of SBA samples [15]. Furthermore, a mismatch repair (MMR) deficiency phenotype was reported in 23% of SBA patients [15]. These findings suggest that the molecular characteristics of SBA are closer to that of CRC than GC, and that molecularly targeted anti-VEGF and anti-EGFR antibodies might be effective for the treatment of SBA. Administration of the anti-VEGF antibody bevacizumab in SBA patients has been reported in several studies [16,17], however the clinical benefit of adding bevacizumab to CT has not yet been ascertained. A single retrospective study of four SBA patients has reported that an irinotecan-based CT combined with anti-EGFR antibody (cetuximab) therapy exhibited a favorable efficacy and safety profile [18], but the clinical benefit of this type of approach for SBA remains to be fully evaluated. In the present study, we determined the efficacy and safety of CT in combination with anti-VEGF antibody, for the treatment of unresectable or metastatic SBA in Japan.

Patients and Methods

Patients

A total of 33 patients with advanced SBA who were treated with more than one regimen of systemic CT, were registered between 1st January 2008 and 31st December 2016 in six different institutions of the Kyushu Medical Oncology Group. All patients were 20 years or older, and had histologically proven adenocarcinoma, mucinous adenocarcinoma, signet-ring adenocarcinoma, or adenosquamous carcinoma of the duodenum, jejunum and ileum. Patients with ampullary tumors were also included. Recurrent cases after surgery were required to have a minimum period of 6 months from the last date of administration of adjuvant CT to the date of confirmation of recurrence. There was no restriction regarding previous therapies for other neoplasms and concurrent active primary cancers. An additional criterion for inclusion was the existence of measurable or evaluable lesions, according to the Response Evaluation Criteria in Solid Tumors guidelines (RECIST ver. 1.1) [19]. The study was approved by the ethics committee of each participating institution, and performed according to the guidelines for biomedical research specified in the Declaration of Helsinki. Because of the retrospective nature of the present study, informed consent was not obtained from each patient.

Clinical variables assessed

Medical information from each patient was retrospectively examined using electronic records. Items surveyed in this study included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumor site (e.g. duodenum, ampullary of Vater, jejunum or ileum), pathohistological diagnosis, *KRAS* mutation status, EGFR and HER2 tumor expression, metastatic and recurrent sites, and disease status. Data relating to previous treatments, including surgery for curative and non-curative intents, bypass surgery, and adjuvant CT were also assessed. Information gathered for systemic CT included the content of CT, PFS and OS statistics, and the reasons for the termination of initial CT. Therapy-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0 [20], and toxicities with CTC-AE Grade 3 or worse were surveyed.

Statistical analysis

PFS was defined as the period from the initiation of therapy to the day of tumor progression determined by each institution, or death from any cause. OS was defined as the period from initiation of CT to the day of death from any cause. The Kaplan-Meier method was used to plot

PFS and OS, with the log-rank test used to assess differences in survival. Correlations between OS and clinical characteristics were analyzed by Spearman's rank correlation analysis and step-wise multivariate regression analysis. The following factors were examined in univariate analysis of OS: age, gender, ECOG PS, tumor location, histological diagnosis, *KRAS* status, disease status, metastatic sites, prior primary tumor resection, serum CEA concentration, serum CA19-9 concentration, and concurrent cancer. Multivariate analysis included factors potentially predictive for the risk of death in univariate analysis. The Mann-Whitney U test was used to analyze the difference in the characteristics of the patients who were treated with bevacizumab-containing CT and those who were treated without bevacizumab. All analyses were two-tailed, with $p<0.05$ considered significant. All statistical procedures were performed using SPSS Statistics software version 21 (IBM Japan, Tokyo, Japan).

Results

Patient background

Thirty-three advanced SBA patients who received CT were assessed. Their median age was 65 years (range, 39-83 years), and the population included 24 men (73%) and nine women (27%)(Table 1). ECOG PS was recorded as '0' in eleven patients (33%), '1' in sixteen patients (49%) and '2' in six patients (18%). Tumors were located in the duodenum in 21 patients (67%), the ampulla of Vater in three patients (9%), the jejunum in seven patients (21%), and the ileum in one patient (3%). Thirty-two patients (97%) were diagnosed with adenocarcinoma, and one patient (3%) with adenosquamous carcinoma. Twenty-two patients (67%) had incurable disease at the initial diagnosis of SBA, and 11 patients (33%) had postoperative recurrence. Among the 23 patients who had prior surgery, 11 received curative surgery and 13 received palliative surgery including bypass surgery. Six patients were treated with surgery followed by adjuvant CT with either modified FOLFOX6 (mFOLFOX6; fluorouracil, leucovorin, and oxaliplatin) (three patients), CAPOX (one patient), UFT (tegafur-uracil) plus leucovorin (two patients), or S-1 (one patient). Metastasized organs included the liver (12 patients, 36%), the lung (three patients, 9%), and the peritoneum (17 patients, 52%). *KRAS* exon 2 mutation status was examined in 18 patients, and was found to be mutated in ten of these cases (56%). Eight patients were examined for EGFR-expression, with seven of these being EGFR-positive and one patient being EGFR-negative. Five patients were examined for HER2-expression, all of which were HER2-negative. Serum concentrations of CEA (carcinoembryonic antigen) were equal to or less than 5 ng/mL in 24 patients (73%), and greater than 5 ng/mL in eight patients (24%); those of CA19-9 (carbohydrate antigen 19-9) were equal to or less than 37 U/mL in 19 patients (59%), and greater than 37 U/mL in 13 patients (39%). Six patients (18%) harbored concurrent cancers.

Efficacies of first-line chemotherapies

First-line CT regimens for the 33 SBA patients were as follows; mFOLFOX6 in thirteen patients (39%), mFOLFOX6 plus bevacizumab in one patient (3%), CAPOX in one patient (3%), and CAPOX plus bevacizumab in three patients (9%); FOLFIRI, irinotecan plus cetuximab, and sLV5FU2 (fluorouracil and leucovorin), were each administered to a single patient; S-1 plus cisplatin was administered to four patients (12%), and S-1 alone to a further four patients (12%); gemcitabine plus cisplatin was administered to two patients (6%), gemcitabine plus S-1 to one patient (3%), and gemcitabine alone to one patient (3%). In the

total cohort, CT was reported as having been terminated due to progressive disease (PD) in 28 patients (85%), decreased PS in one patient (3%), and adverse events in one patient (3%). In one patient CT was terminated for curative surgery, and in another patient, for curative radiotherapy. In one individual the reason for termination of chemotherapy was unknown.

In total, 20 patients with a measurable lesion were evaluable for treatment efficacy. Five patients (25%) achieved partial response (PR), seven (35%) showed stable disease (SD), and eight (40%) showed progressive disease (PD). The objective RR was 25%, and the disease control rate (complete response (CR) + PR + SD) was 60%. Median PFS of the total patients was 6.0 months (Figure 1A), and median OS was 13.0 months (Figure 1B).

In the univariate analysis of clinical characteristics affecting OS, histological diagnosis (p=0.020), *KRAS* gene mutation status (p=0.047) and prior primary tumor resection (p=0.008) were found to be associated with improved OS (Table 2). Multivariate analysis was then performed for these three factors, with prior primary tumor resection (β=0.581, p=0.012) again being significantly associated with improved OS (Table 3).

Therapy and survival of patients treated with molecular targeted therapy

Eleven out of the 33 SBA patients (33%) received the molecularly targeted agents bevacizumab (nine patients; 27%) or cetuximab (three patients; 9%). The nine bevacizumab patients were treated with this agent in the first, second and third treatment lines in combination with mFOLFOX6, CAPOX or FOLFIRI (Table 4). Three patients achieved PR following bevacizumab-containing CT, one patient demonstrated SD, and one patient demonstrated non-CR/non-PD. Median OS of the nine patients who had received bevacizumab in any of the treatment lines (the bevacizumab-treated group) was 21.9 months, while median OS of the 24 patients treated without bevacizumab (the bevacizumab-untreated group) was 11.4 months (p=0.179) (Figure 1C). The clinical characteristics of patients who received bevacizumab-containing CT and those who received CT without bevacizumab were compared (Table 5). Histological diagnosis was significantly different between the groups (p=0.041), but no other significant differences were found between the groups. Grade 3 or 4 adverse events associated with bevacizumab were observed only in a single patient, reported as a grade 3 rectal fistula during treatment with CAPOX plus bevacizumab.

Three patients with *KRAS* wild-type tumors received cetuximab in the first and the third treatment line. Two patients were treated with cetuximab plus irinotecan, and one patient

was treated with cetuximab alone. Two patients achieved SD in response to cetuximab-containing CT.

Treatment after first-line CT

Twenty patients received second-line or additional CT regimens. The second-line CT regimens were as follows: FOLFIRI in five patients, FOLFIRI plus bevacizumab in three patients, irinotecan plus S-1 in two patients, irinotecan alone in two patients, and paclitaxel in four patients; mFOLFOX6, SOX (S-1 and oxaliplatin) plus bevacizumab, S-1 alone, and gemcitabine plus cisplatin, were each administered to a single patient. The median PFS of second-line CT in these patients was 2.5 months. CT treatment beyond third-line was administered to a total thirteen patients.

Discussion

A standard CT approach based on large-scale randomized clinical studies has not yet been established for advanced SBA. Recent prospective phase II studies have shown modest efficacy of first line CAPOX [6], mFOLFOX [7], and CAPOX plus bevacizumab [16] for advanced SBA, with median OS of 15-20 months. A retrospective review of CT efficacy in 93 cases of advanced SBA demonstrated a median PFS of 6.6 months and a median OS of 15.1 months [10]. Although the survival benefits for SBA were slightly poorer than those seen in metastatic CRC [21], combinations of oxaliplatin and fluoropyrimidines have been utilized for advanced SBA based on these findings. It is relevant to note that in the study employing CAPOX [6], 12 of the 30 patients (i.e. 40%) harbored ampullary adenocarcinoma (AAC) and their RR appeared lower than the rate for SBA (33% versus 61%) [6]. In the present study, in which only 9% of the patients had AAC, modest survival benefits were shown, with a median OS of 13.0 months and a median PFS of 6.0 months. The lower proportion of AAC patients in our study might be one of the reasons for more favorable survival data than that seen in the previous phase II study.

Aparicio et al. previously reported that SBA stages I-II, WHO (World Health Organization) PS 0-1, and a MMR-deficiency phenotype, were correlated with longer OS for all patients, and that PS 0-1 and *KRAS* mutation predicted a longer OS for stage IV patients [15]. Other studies have shown that older age, higher tumor stage, poor tumor differentiation, positive resection margins, lymphovascular invasion, lymph node invasion and a low number of recovery lymph nodes, are correlated with poor prognosis [22-24]. Among SBAs, duodenal tumors have been reported to have a worse prognosis than jejunal or ileal tumors [3,5]. In our study, 64% of patients had duodenal tumors, 30% had non-*KRAS* mutated tumors, and 18% had tumors with PS 2, suggesting a relatively unfavorable patient background.

While *KRAS* mutation is identified in around 40% of CRC patients, it is associated with only 3-10% of patients with GC [25-27]. On the other hand, tumor overexpression of HER2 protein is found in around 15% of GC patients, but only 2-3% of CRC patients. Although SBA is generally thought to be a heterogeneous cancer, the high incidence of *KRAS* mutation and rarity of HER2-overexpression suggests that SBA may possess a similar genetic background to that of CRC [15]. In the present study, none of the patients that were examined for HER2 expression showed overexpression of the protein, and 56% of the patients that were assessed for *KRAS* status demonstrated mutation, suggesting that most patients exhibited this previously-reported CRC-like genetic background [15].

SBA often arises in the genetic context of Lynch syndrome [28,29]. A previous study reported that 14 out of 61 SBA patients were identified with MMR-deficiency, and of these, nine were diagnosed with Lynch syndrome [15]. Six out of 33 patients (18%) in our study harbored concurrent cancers, including gastric, colorectal, bladder, gall bladder, ovary, endometrial, and ureteral cancers, and liposarcoma, which (with the exception of liposarcoma) are often observed in patients with Lynch syndrome. One out of these six patients fulfilled the Amsterdam II criteria for the diagnosis of Lynch syndrome [30], while the other five patients possibly have Lynch syndrome with simultaneous occurrence of rare SBA. Since no information regarding MMR genetic alterations or MMR instability in these patients was available, the exact genetic background of these cases cannot be determined. The median OS of the six patients was 10.8 months, which is better than the overall median survival in this study. While SBA with MMR deficiency has been reported to have favorable prognosis [15], concurrent cancer could influence unfavorably on the treatment results for SBA.

Advanced SBA has often been treated with a combination of platinum plus fluorouracil or irinotecan, CT regimens that are employed for both CRC and GC. However, molecularly targeted agents have also been used in the treatment of these diseases. Trastuzumab for HER2-overexpressed GC, and ramucirumab for the second line CT of GC are utilized, but efficacy of bevacizumab in GC has not been proven [31]. The anti-EGFR antibodies, cetuximab and panitumumab, are known to be beneficial for *KRAS* wild-type CRC patients, but not for GC patients. Bevacizumab and ramucirumab are often employed for CRC. Finally, the efficacy of anti-HER2 therapy for HER2-overexpressing CRC has been reported in a phase II clinical trial [32]. However, the effectiveness of these targeted agents in SBA has not been sufficiently evaluated.

Gulhati et al. reported a phase II study evaluating the benefit of adding bevacizumab to CAPOX in patients with SBA and AAC. The median PFS and OS were 8.7 months and 12.9 months, respectively. They compared these results with their previous data of 25 patients in a phase II study, but were unable to determine significant benefits on RR and PFS because of the retrospective nature of the study and the small size of the patient cohort. Finally, the authors concluded that CAPOX with bevacizumab was an active and well-tolerated regimen for patients with SBA and AAC [16].

On the other hand, Aydin et al. reported that the combination of bevacizumab with mFOLFOX6 or FOLFIRI, produced no significant difference in PFS and OS compared with CT alone, in patients with SBA. The median PFS was 7.7 and 9.6 months in the CT alone and the

bevacizumab-containing CT groups, respectively, and the median OS was 14.8 and 18.5 months, respectively [17]. In contrast, several case reports have shown efficacy of bevacizumab-containing CT for SBA [33,34]. Bevacizumab inhibits tumor angiogenesis by specifically binding to VEGF-A. In a study examining VEGF-A expression in 54 SBA patients, 96% of samples were found to be positive [35], suggesting the potential utility of bevacizumab in the treatment of SBA. However, to date, the efficacy of bevacizumab in SBA remains to be proven.

Adverse events, including bleeding and gastrointestinal tract perforation, have been shown for bevacizumab-containing CT in various cancers. In one study, 0.9% of CRC patients treated with bevacizumab showed gastrointestinal tract perforation, from which the mortality rate was 21.7% [36]. Known risk factors for perforation include age ≤ 65 years, no primary tumor resection, and a history of preoperative radiotherapy [37]. Bowel obstruction has also been suggested as a bevacizumab-induced severe adverse event in the patients with ovarian cancer [38]. Since common symptoms of SBA include bowel obstruction and bleeding, bevacizumab treatment may increase the risk of appearance of these symptoms.

In this study, we examined the response of nine SBA patients who had CT in combination with bevacizumab, and observed a more favorable OS than patients treated without bevacizumab. Due to limited patient numbers and the retrospective nature of this study, consideration needs to be given to the possibility of bias in regards to patients with a relatively better condition being preferentially treated with bevacizumab. We thus compared the patient groups treated with or without bevacizumab, thereby only histological diagnosis was significantly different between the groups in their clinical characteristics. More patients with poorly differentiated adenocarcinoma were included in the bevacizumab-untreated group than in the bevacizumab-treated group (33% vs. 11%). We found that surgical resection of the primary tumor was performed more often in the bevacizumab-treated group than in the bevacizumab-untreated group (56% vs. 42%), and that the numbers of patients with ECOG PS 2, and a tumor location in the ampulla of Vater, were less in the bevacizumab-treated group than in the bevacizumab-untreated group, factors that might reflect on prognosis. Seven patients received bevacizumab in second or third line therapies, with PR and SD each observed in one patient, an observation that suggests there may be a modest efficacy of bevacizumab-containing CT in the second or third line treatment of SBA.

Multivariate analysis demonstrated that prior surgical resection of the primary tumor was a favorable factor of better survival in this study. Bevacizumab-containing CT was

administered more often to patients with prior surgical resection of the primary tumor, than those with non-primary resection. Despite this possible bias, the observation suggests that CT in combination with bevacizumab might be beneficial for metastatic SBA. Cetuximab was administered to three *KRAS* wild-type SBA patients in our study, with subsequent SD demonstrated in two of these cases, but because of the small patient population, the survival benefit of this anti-EGFR antibody could not be formally determined. An ongoing phase II clinical study assessing the safety and efficacy of CAPOX plus the anti-EGFR antibody panitumumab, for *KRAS* wild-type SBA and AAC (NCT01202409) will help to determine the clinical benefit of this type of therapeutic approach.

In conclusion, the findings from this retrospective study indicate a potential survival benefit of platinum plus fluoropyrimidine combination therapy for advanced SBA. Moreover, bevacizumab-containing CT was found to be beneficial for these patients. Even though SBA is a rare cancer, continued investigation of the efficacy of molecularly targeted drugs for this disease is warranted.

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Compliance with ethical standards

Conflict of interests

Baba E has received research grants from Chugai and Merck Serono. Akashi K has received research grants from Chugai, Yakult and Merck Serono and an honorarium from Chugai. Esaki T has received a research grant from Merck Serono and honoraria from Chugai and Merck Serono.

Ethical standards

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the ethics committee of each participating institution. For this type of study formal consent is not required.

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Table 1. Patient characteristics

Characteristics	No. of patients (Total n=33)	%
Age, years		
Median (Range)	65 (39-83)	
Gender		
Male	24	73
Female	9	27
ECOG performance status		
0	11	33
1	16	49
2	6	18
Tumor location		
Duodenum	21	67
Ampulla of Vater	3	9
Jejunum	7	21
Ileum	1	3
Small bowel NOS	1	3
Histological diagnosis		
Adenocarcinoma	32	97
Well to moderately differentiated	20	61
Poorly differentiated	9	27
Not specified	3	9
Adenosquamous carcinoma	1	3
KRAS gene status		
Wild-type	8	24
Mutant type	10	30
N/E	15	46
EGFR expression status		
Positive	7	21
Negative	1	3
N/E	25	76
HER2 status		
Positive	0	0
Negative	5	15
N/E	28	85
Disease status		
Unresectable	22	67
Recurrent	11	33
Metastatic site		

Liver	12	36
Lung	3	9
Peritoneum	17	52
Lymph node	17	52
Bone	2	6
Prior primary tumor surgery		
Curative	11	33
Palliative (bypass)	13 (9)	39 (27)
Prior adjuvant chemotherapy		
UFT + LV	2	6
mFOLFOX6	3	9
CAPOX	1	3
S-1	1	3
Serum CEA concentration		
≤5.0ng/mL	24	73
> 5.0ng/mL	8	24
N/E	1	3
Serum CA19-9 concentration		
≤ 37 U/m	19	59
> 37 U/mL	13	39
N/E	1	3
Concurrent cancer		
Yes	6	18
No	27	82

ECOG, Eastern cooperative oncology group; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; EGFR, Epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; N/E, not examined; UFT, tegafur uracil; LV, leucovorin; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; CAPOX, capecitabine and oxaliplatin; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NOS, not otherwise specified.

Table 2. Univariate analysis of clinical characteristics and overall survival

Characteristics	Correlation coefficient	P value
Age	0.017	0.926
Gender	0.171	0.340
ECOG performance status	0.324	0.066
Tumor location	0.117	0.516
Histological diagnosis	0.402	0.020
KRAS status (wild-type/mutant) *	0.474	0.047
Disease status	0.304	0.086
Metastatic site		
Liver	0.198	0.268
Peritoneum	0.045	0.805
Lymph node	0.204	0.255
Prior primary tumor resection (yes/no)	0.454	0.008
Serum CEA concentration**	0.047	0.799
Serum CA19-9 concentration**	0.203	0.264
Concurrent cancer (yes/no)	0.025	0.891

*N=18; **N=32; Coefficients and p-values derived from Spearman's rank correlation analysis; ECOG, Eastern cooperative oncology group; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; CEA, carcinoembryonic antigen (≤ 5.0 ng/mL or > 5.0 ng/mL); CA19-9, carbohydrate antigen 19-9 (≤ 37 U/mL or > 37 U/mL).

Table3. Multivariate analysis of clinical characteristics and overall survival

Items	β	P value
Histological diagnosis		0.253
KRAS status		0.144
Priory primary tumor resection	0.581	0.012

15 patients were excluded because they had no *KRAS* status data. Of the remaining patients, 18 were selected for multivariate analysis. The standardized partial regression coefficient (β) were calculated by step-wise multivariate regression; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog.

Table 4. Therapy and survival of patients treated with bevacizumab-containing therapy

Patient	Treatment Line	Combination Chemotherapy	Response	PFS (months)	OS (months)
1	1st	mFOLFOX6	PR	16.9	21.8
	2nd	FOLFIRI	PD	2.1	
2	1st	CAPOX	NE	15.7	21.9
	2nd	SOX	PR	15.0	
3	1st	CAPOX	PR	13.4	16.7
4	1st	CAPOX	Non-CR/Non-PD	-	36.3 (alive)
5	2nd	FOLFIRI	SD	6.2	38.0
6	2nd	FOLFIRI	PD	2.5	9.2
7	3rd	mFOLFOX6	PD	1.8	13.1
8	3rd	FOLFIRI	PD	5.3	29.6
9	3rd	FOLFIRI	PD	1.8	14.9

PFS, progression-free survival; OS, overall survival; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; CAPOX, capecitabine and oxaliplatin; SOX, S-1 and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not examined.

Table 5. Comparison between patient groups treated with or without bevacizumab

Characteristics	No. of patients		P value
	With Bev (N=9)	Without Bev (N=24)	
Age, years Median (Range)	60 (48-67)	67 (39-83)	0.266
Gender			0.637
Male	6	6	
Female	3	18	
ECOG performance status			0.367
0	4	7	
1	4	12	
2	1	5	
Tumor location			0.925
Duodenum	6	15	
Ampulla of Vater	0	3	
Jejunum	2	5	
Ileum	0	1	
Small bowel NOS	1	0	
Histological diagnosis			0.041
Adenocarcinoma			
Well to moderately differentiated	8	12	
Poorly differentiated	1	8	
Not specified	0	3	
Adenosquamous carcinoma	0	1	
KRAS gene status			0.916
Wild-type	3	5	
Mutant type	4	6	
Disease status			0.414
Unresectable	5	17	
Recurrence	4	7	
Metastatic site			
Liver	4	8	0.561
Peritoneum	5	12	0.779
Lymph node	4	13	0.624
Prior primary tumor resection	5	10	0.482
Prior adjuvant chemotherapy	3	4	0.304
Serum CEA concentration > 5.0ng/mL	2	6	0.870
Serum CA19-9 concentration > 37 U/mL	4	9	0.720

The Mann-Whitney U test was used to analyze the difference in the characteristics of the patient groups. Bev, Bevacizumab; ECOG, Eastern cooperative oncology group; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NOS, not otherwise specified.

Figure.1

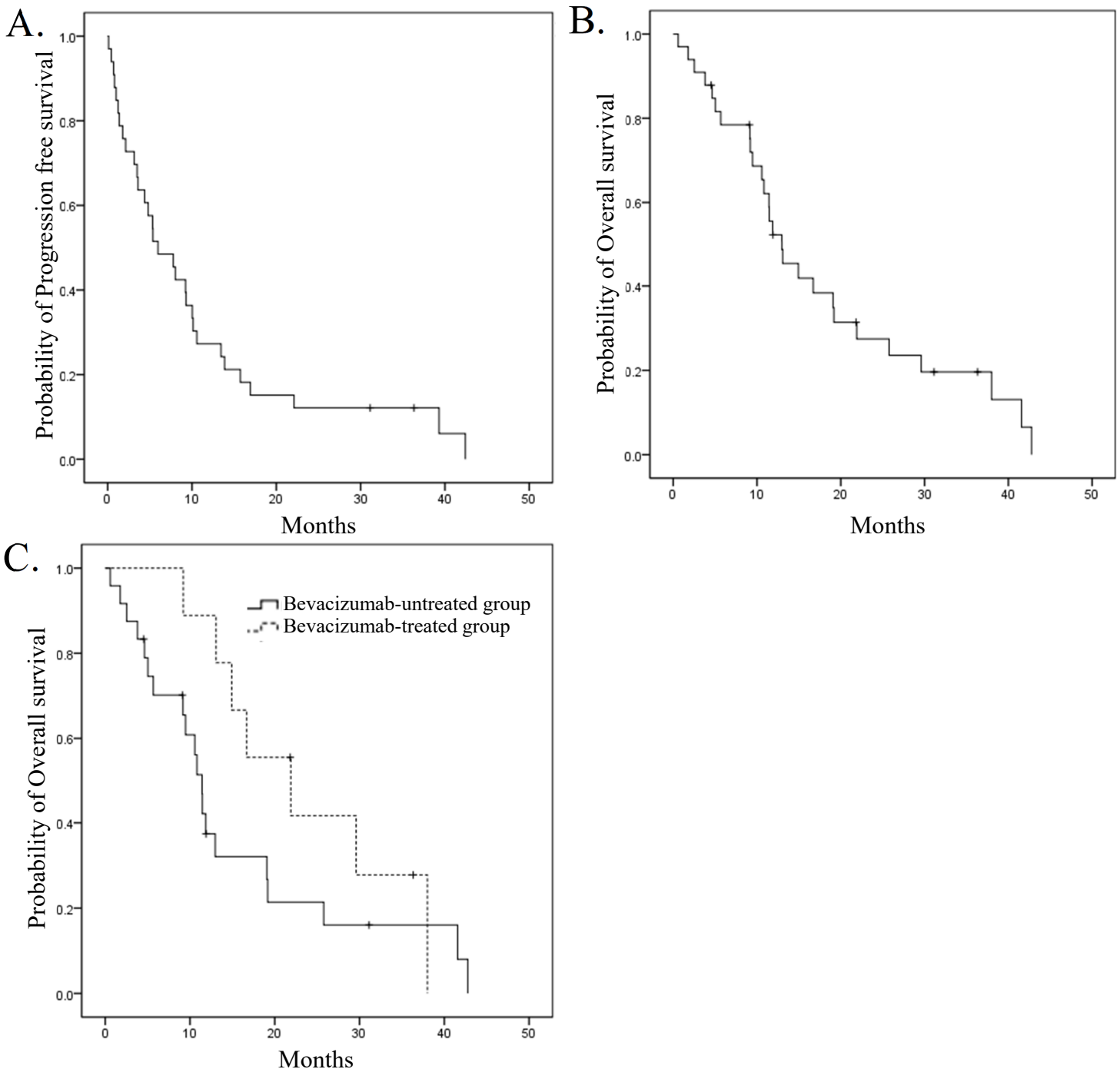

Figure legends

Figure 1. Kaplan-Meier plots for progression-free (PFS) and overall (OS) patient survival. (A) PFS curves for patients treated with first-line CT; (B) OS curves for patients treated with first-line CT; (C) OS curves for patients treated with or without the inclusion of bevacizumab.