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ORIGINAL ARTICLE

Efficacy of the FOLFOX/CAPOX regimen for advanced small bowel adenocarcinoma: A three-center study from China

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Summary

Purpose: *Small bowel adenocarcinoma (SBA) is a rare malignancy, and most patients present with unresectable or metastatic disease. Thus far, no standard chemotherapeutic regimen has been established and related data are scarce, especially in Eastern countries. The purpose of this multicenter study was to evaluate the efficacy and toxicity of oxaliplatin combined with fluoropyrimidines in Chinese patients with advanced SBA.*

Methods: *Advanced SBA patients who received FOLFOX (5-fluorouracil/5-FU plus leucovorin and oxaliplatin)/CAPOX (capecitabine plus oxaliplatin) as first-line chemotherapy between February, 2004 and October, 2010 were identified from 3 large medical centers in China. The response rate (RR), progression-free survival (PFS), overall survival (OS), and chemotherapy-associated toxicity were evaluated. Cox models were applied for multivariate analyses.*

Results: *Of 34 patients, with SBA 28 received FOLFOX and 6 CAPOX. The objective response (OR) and disease control (DC) rates were 32.3% and 61.7%, respectively. The median PFS and OS were 6.3 and 14.2 months, respectively. The toxicity was tolerable, grade 3-4 toxicity was rare. In multivariate analysis, only multi-organ metastasis reached borderline significance for shorter PFS (p=0.059), but the variables of age (>65 years; p=0.001), and multi-organ metastasis (p=0.001) were significantly associated with poor OS.*

Conclusion: *To our knowledge, this multicenter retrospective study is the first and largest one among Asian studies at present estimating oxaliplatin combined with fluoropyrimidines as first-line chemotherapy for advanced SBA. FOLFOX/CAPOX is proved effective for advanced SBA in this study, but the results do not absolutely agree with previous studies from Western countries, showing that further studies are still needed.*

Key words: advanced small bowel adenocarcinoma, CAPOX, chemotherapy, FOLFOX, oxaliplatin

Introduction

SBA is a rare malignancy of the gastrointestinal tract but the most common histological subtypes of small bowel malignant tumors and their outcomes are poor [1]. The 5-year survival rates for all the stages and stage IV SBA patients were reported to be less than 30% and less than 5%, respectively [2,3]. Although the incidence of SBA is much lower than that of other malignancies of the digestive tract, it is increasing in recent years, especially among men [4-6]. Because of its nonspecific clinical symptoms as well as its distal position, which leads to failure of early diagnosis, most cases are detected in unresectable or metastatic stage. Even if the condition is detected in stages I-III, many patients have regional recurrence or distant metastasis after surgery.

Systemic chemotherapy is necessary for the treatment of SBA. However, no standard chemotherapeutic regimen has been recommended for advanced SBA, and treatment-related data are limited. Some retrospective

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studies from Western countries have shown survival benefit with palliative chemotherapy for SBA as compared to no treatment or best supportive care [3,7,8]. Because physicians lack treatment experience for SBA and because of the similar histological features of SBA and large intestinal or gastric cancer, SBA treatment is always deduced from the management of large intestinal or gastric cancer. One retrospective study suggested that the combination of 5-fluorouracil (5-FU) and a platinum compound yields a higher response rate and longer PFS than other chemotherapeutic regimens for advanced SBA [9]. FOLFOX is the most effective first-line chemotherapeutic choice for colorectal adenocarcinoma [10,11]. Capecitabine, as an orally administered 5-FU formulation, is commonly used in the treatment of gastrointestinal cancer. CAPOX had been demonstrated to be as effective as FOLFOX as first-line therapy for colorectal cancer [12-16]. Two studies from Western countries showed that FOLFOX and CAPOX were effective for SBA treatment [17,18], suggesting that either regimen could be recommended as the standard choice of first-line chemotherapy for SBA.

However, efficacy data are still limited, especially for patients from the East. A study from Japan evaluated the efficacy of irinotecan combined with cisplatin (IP) for 8 advanced SBA patients, and showed a RR of 12.5%, and median OS 17.3 months [19]. Another Asian study from Korea reported the overall efficacy of various regimens for the treatment of 34 advanced SBA patients; the RR was 27.6%, and median OS 9.0 months, but the specified regimens were not given [20]. Until now, no data on FOLFOX or CAPOX for advanced SBA could be obtained from Asian studies.

The purpose of the current multicenter retrospective study was to evaluate the efficacy and toxicity of FOLFOX/CAPOX as first-line regimen in Chinese patients with advanced SBA.

Methods

Three large medical centers (Sun Yat-Sen University Cancer Center, The First People's hospital of Foshan, and Sun Yat-Sen Memorial hospital of Sun Yat-Sen University) participated in this retrospective study. The cases of all consecutive patients diagnosed with small bowel tumor between February 2004 and October 2010 were retrospectively reviewed.

Inclusion/exclusion criteria

Only the following patients were included: (1) those with histologically confirmed unresectable or metastatic SBA, and evaluable disease; (2) those who had received at least 1 cycle of FOLFOX or CAPOX as first-line treatment; and (3) those who had no concomitant severe non-cancer diseases or other concomitant cancers. Patients with primary ampullary adenocarcinoma were excluded.

Chemotherapy

FOLFOX was given as follows: 85 mg/m^2 oxaliplatin (OXA) in a 3-h infusion, 400 mg/m^2 leucovorin (LV) in a 2-h infusion, then 400 mg/m^2 5-FU bolus, followed by 2.4-3.0 g/m^2 5-FU as a 46-h infusion. This regimen was repeated every 2 weeks. CAPOX was given as follows: day 1, 130 mg/m^2 OXA in a 3-h infusion, 1000 mg/m^2 oral capecitabine twice daily days 1-14 of each treatment cycle. This regimen was repeated every 21 days.

Histological grading was determined according to the pathology reports, and response assessment and chemotherapy toxicity grading were based on the records of computerized tomography (CT) scan and the treating doctor's assessment records. All patients who had received at least 1 cycle of chemotherapy were included in the toxicity assessment. PFS and OS were defined as the time between the beginning of treatment and the time of progression or death, respectively. The date of last follow-up was recorded as censored data for survival analysis when the time of death or progression could not be confirmed or if the patient was still alive.

Statistical analysis

All data on clinical characteristics, response rates, and toxicities were examined using the statistical software SPSS 13.0; PFS, OS, and median follow-up and survival curves were assessed or drawn using the Kaplan-Meier method. Univariate and multivariate analyses (Cox regression) were used to find predictors of survival. The following predefined variables were examined in univariate analyses of PFS and OS: sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), pathology diagnosis, previous treatments (surgery or adjuvant chemotherapy), metastatic status, metastatic sites, primary tumor site, baseline serum carcinoembryonic antigen (CEA) level (2-fold the upper limit of normal, 10 ng/mL), and baseline serum carbohydrate antigen 19-9 (CA19-9) level (2-fold the upper limit of normal, 70 U/mL). Multivariate analysis included variables potentially predictive of disease progression or death in univariate analysis. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

The medical records of 249 SBA patients were retrospectively reviewed and 34 of them meeting the inclusion criteria were enrolled into this study. The patient demographic and clinical characteristics are shown in Table 1. Their median age was 56 years (range 23-73), and, as was reported in other studies, most patients were male (n=27, 79.4%). Patients with ECOG PS ≥ 2 comprised 23.5% of the studied group. In 32 (94.1%) patients, the primary tumor site was located in the duodenum; in one, it was located in the jejunum and in another one in the ileum. Seventeen patients (50%) had well or moderately differentiated adenocarcinoma, 14 (41.2%) had poorly or non-differentiated adenocarcinoma, and 3 had adenocarcinoma of unknown grade. Of the 34 patients, 19 (59.9%) were diagnosed with metastatic disease at first presentation, 12 (35.3%) developed metastatic disease after curative surgery, and 3 (8.8%) had locally advanced disease. Six (17.6%) patients had multi-organ metastatic disease, with liver being the most common metastatic site (n=12; 35.3%), followed by distant lymph nodes (23.5%), peritoneum or abdominal wall (14.7%), and lung (14.7%). Before palliative chemotherapy, 27 patients underwent surgery: 15 (44.1%) underwent palliative or exploratory surgery and 12 (35.3%), curative surgery. Two patients (5.8%) received adjuvant chemotherapy after curative surgery and 7 (20.6%) never received any prior treatment. Thirteen patients received second-line chemotherapy after disease progression: 5 received irinotecan-based therapy (FOLFIRI); 3 gemcitabine-based therapy; 2 paclitaxel-based therapy; 2 hydroxycamptothecin-based therapy; 1 ifosfamide (IFO) combined with etoposide (VP-16); and 1 re-initiated FOLFOX therapy more than one year later.

Table 1. Patient characteristics

Characteristics	*Patients, n*	*%*
Sex		
Male	27	79.4
Female	7	20.6
Age (years)		
Median	56	
<40	4	
40-60	24	11.8
>60	6	70.6
ECOG PS		17.6
0/1	26	
2	7	76.5
3	1	20.6
Tumor primary site		
Duodenum	32	94.1
Jejunum+ ileum	2	5.9
Grade (adenocarcinoma)		
Well - moderately differentiated	17	50.0
Poorly or not differentiated	14	41.2
NOS	3	8.8
Metastatic status		
Locally advanced	3	8.8
Primary metastatic	19	59.9
Secondary metastatic	12	35.3
Metastatic sites		
Locally advanced	3	8.8
Distant lymph nodes	8	23.5
Liver	12	35.3
Lung	5	14.7
Peritoneum or abdominal wall	5	14.7
Multi-organ	6	17.6
Prior treatment		
No treatment	7	20.6
Radical surgery	12	35.3
Palliative or exploratory surgery	15	44.1
Adjuvant chemotherapy	2	5.9
Baseline of CEA level (ng/ml)		
≤5	18	52.9
>5	14	41.2
Unknown	2	5.9
Baseline of CA19-9 level (U/ml)		
≤35	11	32.4
>35	20	58.8
Unknown	3	8.8

ECOG: Eastern Cooperative Oncology Group, PS: performance status, NOS: not otherwise specified, CEA: carcinoembryonic antigen, CA: carbohydrate antigen

Response, survival and multivariate analysis

Twenty-eight patients received FOLFOX6 and 6 received CAPOX as first-line treatment. The median number of chemotherapy cycles received was 4.5 (range 1-12). Response could be evaluated in all 34 patients. Partial response (PR), stable disease (SD), OR, and DC rates were 32.3, 29.4, 32.3, and 61.7%, respectively (Table 2).

The median follow-up time was 17.9 months (range 1.7-74.1), and the PFS and OS curves showed a median PFS of 6.3 months (95% CI 3.3-9.4; Figure 1), and a median OS of 14.2 months (95% CI 10.8-17.5; Figure 2).

Among the 2 potentially predictive variables for

Table 2. Tumor response rates

Response	*Patients, n*	*%*
CR	0	0.0
PR	11	32.3
SD	10	29.4
PD	13	38.2
NA	0	0.0
ORR		32.3
DCR		61.7

CR: complete response, PR: partial response, SD: stable disease, PD: disease progression, NA: not available, ORR: objective response rate, DCR: disease control rate

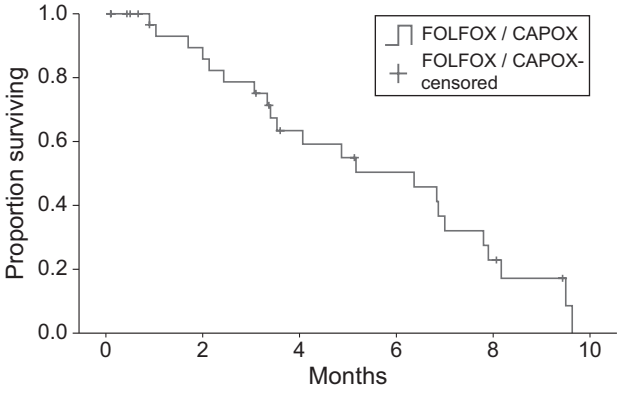

Figure 1. Kaplan-Meier curve for progression-free survival. The median PFS was 6.3 months (95% confidence interval, 3.3-9.4).

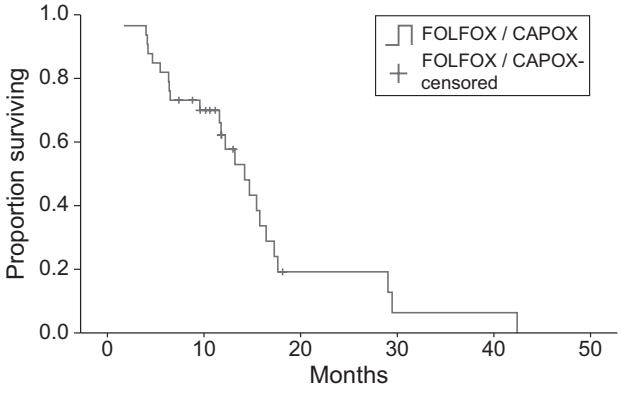

Figure 2. Kaplan-Meier curve for overall survival. The median OS was 14.2 months (95% confidence interval, 10.8-17.5).

PFS selected by univariate analysis (PS, p=0.04 and multi-organ metastasis, p=0.01; Table 3), only multi-organ metastasis reached a p value of borderline significance for PFS in the multivariate analysis. And patients with multi-organ metastasis seemed to have poorer PFS (3.0 vs. 6.8 months, p=0.059; Table 4).

Table 3. Univariate analysis of factors associated with PFS and OS

Factors	*PFS (months)*	*p-value*	*OS (months)*	*p-value*
Sex		0.49		0.31
Female	5.1		14.2	
Male	6.8		NA	
Age (years)		0.24		0.002
≤65	NA		15.4	
>65	NA		4.2	
ECOG PS		0.04		0.10
0-1	6.8		15.4	
≥2	3.1		9.5	
Grade		0.24		0.59
Well-moderately differentiated	6.8		13.2	
Poorly or not differentiated	4.0		14.7	
Prior surgery		0.15		0.99
No	6.3		11.7	
Radical	8.0		13.2	
Exploratory or palliative	4.0		14.2	
Adjuvant chemotherapy (yes / no)	0.9/6.3	0.37	6.4/14.2	0.75
Metastatic status		0.26		0.61
Locally advanced	8.1		29.4	
Primary metastatic	5.1		14.7	
Secondary metastatic	6.8		13.2	
Metastatic sites (yes / no)				
Locally advanced	8.1/5.1	0.19	29.4/14.2	0.19
Distant lymph node	6.8/4.8	0.78	14.7/14.2	0.67
Liver	4.8/6.3	0.67	13.2/14.7	0.35
Lung	6.8/5.1	0.38	14.2/13.2	0.68
Peritoneum or abdominal wall	4.0/6.8	0.37	15.4/13.2	0.79
Multi-organ	3.0/6.8	0.01	4.1/14.7	0.001
Primary tumor site		0.26		0.37
Duodenum	6.8		NA	
Jejunum or ileum	3.0		NA	
Baseline CEA level (ng/ml)		0.96		0.058
≤ 10	6.8		15.4	
> 10	4.8		9.5	
Baseline of CA19-9 level (U/ml)		0.42		0.67
≤ 70	6.8		14.7	
> 70	5.1		15.7	

NA: not available, PFS: progression-free survival, OS: overall survival

Table 4. Multivariate analysis of factors associated with PFS and OS

Factors	*PFS (months)*	*p-value*	*OS (months)*	*p-value*
Age (years)				0.001
≤ 65			15.4	
>65			4.2	
ECOG PS		0.122		0.486
0-1	6.8		15.4	
≤ 2	3.1		9.5	
Metastatic sites (yes / no)				0.001
Multi-organ	3.0/6.8	0.059	4.1/14.7	

PFS: progression-free survival, OS: overall survival

Two potentially predictive variables for OS were selected by univariate analysis: age (p = 0.002), multi-organ metastasis (p=0.001; Table 3). Both were independently associated with significantly poorer OS in multivariate analysis: age (>65 vs. ≤65 years, p = 0.001), multi-organ metastasis (p=0.001; Table 4).

Toxicity

All patients were evaluated for toxicity, and most of the chemotherapy-associated toxicities were found to be of low grade (Table 5). The most common hematologic grade 1-2 toxicities were neutropenia (26.5%, n = 9), followed by thrombocytopenia (11.7%, n = 4) and anemia (8.8%, n = 3), while the most common non-hematologic grade 1-2 toxicities were of gastrointestinal origin (anorexia 58.8%; nausea 47.1%; vomiting 29.4%; diarrhea 14.7%), followed by peripheral neuropathy (41.2%) and alopecia (11.7%). Grade 3-4 toxicities were rare, and hematologic toxicities were more common than non-hematologic ones. Among the hematologic toxicities, grade 3 neutropenia was observed in 3 patients, grade 4 thrombocytopenia in 1, and grade 3 anemia in 1. No febrile neutropenia or thrombocytopenia-associated hemorrhagic events were recorded. With regard to non-hematologic toxicities, only 1 patient had grade 3 diarrhea, which subsided after symptomatic treatment.

Discussion

SBA is usually discovered at advanced stages and chemotherapy is the main treatment option for these patients, but up until now data on chemotherapy are scarce (Table 6). In 1965, Rochlin et al. first reported the efficacy of single-agent treatment with 5-FU for SBA. Four of the 11 patients in their study responded to 5-FU [21]. Thereafter, some small retrospective studies reported their results on the use of 5-FU-based regimens for SBA treatment and showed a median OS of 8-13 months and an overall RR of 0%-37% [7,22-26]. Thus far, several retrospective studies have demonstrated the benefit of palliative chemotherapy for SBA. In a retrospective

Table 5. Chemotherapy-associated toxicities

Toxicity	*Grade 1-2*		*Grade 3-4*	
	No. (total=34)	*%*	*No. (total=34)*	*%*
Hematologic				
Neutropenia	9	26.5	3	8.0
Neutropenic fever	0	0.0	0	0.0
Anemia	3	8.8	1	2.9
Thrombocytopenia	4	11.7	1	2.9
Non-hematologic				
Anorexia	20	58.8	0	0.0
Nausea	16	47.1	0	0.0
Vomiting	10	29.4	0	0.0
Stomatitis	1	2.9	0	0.0
Diarrhea	5	14.7	1	2.9
Fatigue	1	2.9	0	0.0
Alopecia	4	11.7	0	0.0
Liver function damage	1	2.9	0	0.0
Peripheral neuropathy	14	41.2	0	0.0
Digestive tract hemorrhage	1	2.9	0	0.0

Table 6. Studies of systemic chemotherapy in SBA

First author	*Year*	*Study type*	*Patients, n*	*Regimen*	*RR (%)*	*OS (months)*
Zaanan [18]	2010	Retrospective	48	FOLFOX	34.0	17.8
			10	LV5-FU2	0.0	13.5
			19	FOLFIRI	9.0	10.6
			16	LV5-FU2+cisplatin	31.0	9.3
Suenaga [28]	2009	Retrospective	10	5-FU	10.0	12.0
Moon [20]	2009	Retrospective	34	Various	27.6	9.0
Overman [17]	2008	Prospective phase II	30	CAPOX	50.0	20.4
Ono [19]	2008	Retrospective	8	Cisplatin+irinotecan	12.5	17.3
Overman [9]	2008	Retrospective	29	5-FU+platinum	41.0	14.8
			51	Other regimens	16.0	12.0
Czraykowski [8]	2007	Retrospective	16	5-FU based regimens	6.0	15.6
Fishman [7]	2006	Retrospective	44	Various regimens	29.0	11.1
Locher [23]	2005	Retrospective	20	5-FU+platinum	21.0	14.0
Gibson [27]	2005	Prospective phase II	38	5-FU+MMC+doxorubicin	18.0	8.0
Goetz [29]	2003	Prospective phase I	5	5-FU+cisplatin+irinotecan	40.0	NR
Crawley [22]	1998	Retrospective	8	5-FU based regimens	37.0	13.0
Jigyasu [24]	1984	Retrospective	14	5-FU based regimens	7.0	9.0
Ouriel [25]	1984	Retrospective	14	5-FU based regimens	NR	10.7
Morgan [26]	1977	Retrospective	7	5-FU based regimens	0.0	NR
Rochlin [21]	1965	Retrospective	11	5-FU single agent	36.0	NR

RR: response rate, OS: overall survival, SBA: small bowel adenocarcinoma

study, Dabaja and colleagues demonstrated that chemotherapy of patients with inoperable or metastatic SBA yielded a better median OS over no chemotherapy (12 vs. 2 months, p=0.02) [3]. Another retrospective study by Czaykowski and Hui showed that the median OS seemed to double (15.6 vs 7.7 months) in patients receiving palliative chemotherapy compared to those receiving no chemotherapy [8].

Nonetheless, no standard regimen is available for frontline chemotherapy of advanced SBA, and physicians deduce most used regimens from their experience coming from gastric or colorectal cancers. Only 2 prospective studies on chemotherapy for advanced SBA have been reported thus far: in 2005, a multicenter phase II prospective study conducted by ECOG reported the combination of 5-FU, doxorubicin, and mitomycin C (FAM) for treatment of SBA or adenocarcinoma of the ampulla of Vater in 39 patients. The overall RR was 18%, and the median OS 8 months [27]. In 2008, a single-center retrospective study conducted by the MD Anderson Cancer Center (MDACC) indicated that 5-FU combined with a platinum regimen (n=29) yielded a higher response rate than other regimens (n=51) (46 vs. 16%, p = 0.01). The median OS, too, was longer with the former regimen, although the difference was not statistically significant (14.8 vs. 12 months, p = 0.1) [9]. In the MDACC study, 6 patients received combination of 5-FU+OXA, and 4 of them responded. In 2009, the same group reported a prospective single-center phase II study of capecitabine combined with oxaliplatin (CAPOX) used as first-line chemotherapy for advanced SBA and adenocarcinoma of the ampulla of Vater in 30 patients. The results showed a high response rate of 50%, median time to progression (TTP) of 11.3 months, and median OS of 20.4 months, results that were very encouraging [17]. In their study, patients diagnosed with advanced ampulla adenocarcinoma were included and most of the patients had good PS before therapy. Recently, Zaanan et al. published their multicenter retrospective study on the FOLFOX regimen as frontline chemotherapy for SBA. They found that the OR, PFS, and OS rates of FOLFOX (n = 48), LV5-FU2 (n=10), FOLFIRI (n=19), and LV5-FU2-cisplatin (n = 16) were 34, 0, 9, and 31% (p = 0.18); 6.9, 7.7, 6.0, and 4.8 months (p=0.16); and 17.8, 13.5, 10.6, and 9.3 months (p=0.25), respectively. FOLFOX was found to be superior to the regimens with leucovorin, 5-FU and cisplatin with statistical significance (PFS=6.9 vs. 4.8 months, p=0.02; OS=17.8 vs. 9.3, p=0.04) [18], indicating that SBA was more sensitive to oxaliplatin than cisplatin. Therefore, they suggested that FOLFOX might be a good choice for the treatment of advanced SBA.

However, data on FOLFOX or CAPOX for the treatment of SBA remain limited. In the present study, FOLFOX and CAPOX proved effective, but the median PFS (6.3 months) and OS (14.2 months) were shorter than those in the study reported by Overman et al. (TTP 11.3 months, OS 20.4 months) [17]. In addition, Zaanan et al. showed better PFS and OS rates than ours (PFS 6.9 months, OS 17.8 months) [18]. Upon reviewing the data, we identified some possible reasons for these differences: first, 23.5% of the patients in our study

showed worsened PS (≥2) before the first line chemotherapy, which is more than in the 2 prior studies, and PS was identified as an independent prognostic factor for advanced SBA in previous studies [7,18]; second, 94.1% of the patients in this study had duodenal adenocarcinoma, and survival analysis in 2 previous studies showed that duodenal adenocarcinoma had worse outcomes than jejunal or ileal adenocarcinoma [2,3]; third, the median number of chemotherapy cycles administered in the present study (4.5) was less than that in the aforementioned studies (10 [18] and 5 [17]), and this may have affected OS. In addition to disease progression, the stopping of chemotherapy was also affected by several other reasons in this study, which contained heavy economic burden and patients' poor compliance to chemotherapy-related toxicities, such as alopecia and vomiting. In some patients, the chemotherapy records were lost when patients changed hospitals during the treatment period before disease progression and some patients had delayed comparative CT scans performed after stopping chemotherapy, which could explain the discrepancy between median chemotherapy cycles (4.5) and median PFS (6.3 months). Furthermore, the small sample and the retrospective nature of our study might also contribute to the survival difference. However, although the reasons mentioned above could be the main cause for the survival difference, we could not absolutely exclude the possibility of different efficacy between the patients from East and West, so further studies are still needed.

In this study, older age (>65 years) was a significant predictor of poor OS in the multivariate analysis, a result which is consistent with previous studies [2]. Moreover, multi-organ metastasis was also identified as a significant predictor of poor OS (p=0.001), which was a new finding in our study. But our results must be interpreted with caution and externally validated as results of a small sample.

Yet, FOLFOX or CAPOX were well tolerated by the patients in this study, and grade 3-4 toxicities were not as common as in other studies, which may be explained by the fewer chemotherapy cycles or incomplete patient records or the good tolerance of Asian patients. However, even the common toxicities, including gastrointestinal side effects, neutropenia, and peripheral neuropathy, were tolerable.

In summary, to our knowledge, this multicenter retrospective study is the first and largest one among Asian studies of oxaliplatin combined with fluoropyrimidines as first-line chemotherapy for advanced SBA. FOLFOX/CAPOX proved effective for unresectable or metastatic SBA in this study, but the results do not absolutely agree with those of previous studies from Western countries [17,18]. FOLFOX/CAPOX could be the treatment of choice for unresectable or metastatic SBA, but further studies are still needed.

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