The characteristics and outcomes of small bowel adenocarcinoma: a multicenter retrospective observational study

Running title: Small bowel adenocarcinoma outcomes

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Abstract

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy that accounts for 1-2% of gastrointestinal tumors. We investigated the clinical characteristics, outcomes, and prognostic factors of primary SBA.

Methods: We retrospectively analyzed the characteristics and clinical courses of 205 SBA patients from 11 institutions in Japan between June 2002 and August 2013.

Results: The primary tumor was in the duodenum and jejunum/ileum in 149 (72.7%) and 56 (27.3%) patients, respectively. Sixty-four patients (43.0%) with duodenal adenocarcinoma were asymptomatic and most cases were detected by esophagogastroduodenoscopy (EGD), which was not specifically performed for the detection or surveillance of duodenal tumors. In contrast, 47 patients (83.9%) with jejunoileal carcinoma were symptomatic. The 3-year survival rate for Stage 0/I, II, III, and IV cancers was 93.4%, 73.1%, 50.9%, and 15.1%, respectively. Multivariate analysis revealed performance status 3-4, high carcinoembryonic antigen (CEA), high lactate dehydrogenase (LDH), low albumin, symptomatic at diagnosis, and Stage III/IV disease were independent factors for overall survival (OS). Ten patients (18.5%) with Stage IV disease were treated with a combination of resection of primary tumor, local treatment of metastasis, and chemotherapy; this group had a median overall survival of 36.9 months.

Conclusions: Although most SBA patients were diagnosed with symptomatic, advanced stage disease, some patients with duodenal carcinoma were detected in early stage by EGD. High LDH and symptomatic at diagnosis were identified as novel independent prognostic factors for OS. The prognosis of advanced SBA was poor, but combined modality therapy with local treatment of metastasis might prolong patient survival.

Keywords: small bowel, small intestine, adenocarcinoma

Introduction

The small intestine accounts for 75% of the length and 90% of the absorptive surface of the gastrointestinal tract. Fortunately, despite the large surface area, the incidence of malignant small bowel tumors is low and makes up less than 5% of all gastrointestinal tumors [Neugut et al, 1998; Overman, 2009; Aparicio et al, 2014]. Small bowel adenocarcinoma (SBA) is one of the most common histological subtypes that accounts for approximately 40% of malignant small bowel tumors [Bilimoria et al, 2009]. According to the EUROCARE data, the incidence of SBA is estimated at approximately 3,600 new cases per year in Europe [Faivre et al, 2012].

Surgical resection with regional lymph node dissection is considered the standard therapy for localized and resectable disease. Long-term survival can be expected if curative resection is possible, but curative resection is often not feasible in patients with SBA, as this cancer is difficult to detect in the early stages of disease, and most cases are diagnosed in the advanced stage [Dabaja et al, 2004]. Although some reports have identified a survival benefit of systemic chemotherapy for patients with advanced SBA, its treatment outcome is not sufficient [Overman, 2009; Aparicio et al, 2014; Zaanan et al, 2010]. Therefore, the prognosis of all stages remains poor and the 5-year overall survival (OS) rate is around 30%, with a median OS time of approximately 19 months [Aparicio et al, 2014]. Several studies have investigated the prognostic factors of SBA. These have identified advanced age, poorly differentiated carcinoma, T4 tumor stage, and duodenal primary site as important prognostic factors [Bilimoria et al, 2009; Dabaja et al, 2004; Zaanan et al, 2010; Talamonti et al, 2002; Halfdanarson et al, 2010; Fishman et al, 2006; Koo et al, 2011; How et al, 1999; Wu et al, 2006; Hong et al, 2009].

Since primary adenocarcinoma of the small intestine is rare, most previous studies were retrospective and conducted in single tertiary care centers. Data of these studies were potentially limited by selection bias, and may not accurately reflect true SBA status. On the other hand, some registry database studies, with large datasets and reduced risk of selection bias, have been conducted; however, may lack detailed data. In this study, we conducted a multicenter observational study to clarify the clinical characteristics, current status, prognostic factors, and outcome of primary SBA.

Materials and Methods

Patients

This multicenter retrospective study included a total of 205 patients who were diagnosed with adenocarcinoma of the small intestine at the following 11 hospitals from June 2002 and August 2013: Okayama University Hospital, Kurashiki Central Hospital, Okayama Saiseikai General

Hospital, Hiroshima City Hiroshima Citizens Hospital, Shikoku Cancer Center, Japanese Red Cross Okayama Hospital, Kagawa Prefectural Hospital, Mitoyo General Hospital, Japanese Red Cross Society Himeji Hospital, Tsuyama Chuo Hospital, and Sumitomo Besshi Hospital.

Data Collection

Data of patients with small intestinal tumors with a histological diagnosis of adenocarcinoma were included in this study. Exclusion criteria were: 1) tumor located on ampulla of Vater, 2) suspected invasive tumor of the pancreas, and 3) small intestinal metastasis from the cancer of other organs. Patients' medical records were reviewed and the following clinico-pathologic parameters were collected: gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), site of primary tumor, predisposing conditions, histological type, symptoms at diagnosis, Union for International Cancer Control (7^{th} ed.) cancer stage based on the tumor, nodes, metastasis (TNM) classification, blood examination dates (carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), hemoglobin (Hb), neutrophil-to-lymphocyte rate (NLR), platelet (Plt), alanine aminotransferase (ALT), creatinine (Cr), lactate dehydrogenase (LDH), albumin (Alb), sodium (Na)), treatment, and survival. We investigated the clinical features, overall survival, and prognostic factors.

Statistical Analysis

All continuous variables are reported as median (range), and all categorical variables are summarized as frequencies (percentages). The Wilcoxon rank sum test was used to compare continuous variables. The chi-square test or Fisher's exact test was used to compare categorical variables. Overall survival was estimated by the Kaplan-Meier method and the difference was evaluated using the log-rank test. Cox proportional hazard model was used to identify independent prognostic factors for OS. All tests were two-sided, and a p-value under 0.05 was considered statistically significant. Statistical analyses were performed using JMP® 11 (SAS Institute Inc, Cary, NC, USA).

Results

Patient Characteristics

Two-hundred and five patients from the 11 institutions were included. Patient characteristics are summarized in Table 1. Median age was 68 years (range, 29-89), and 147 patients (71.7%) were men. Only three patients had predisposing conditions; 1 patient had familial adenomatous polyposis (FAP), 1 patient had Crohn's disease, and 1 patient had Lynch syndrome.

The location of the primary tumor was in the duodenum and jejunoileum in 149 (72.7%), and 56 (27.3%) patients, respectively. The histological type was undifferentiated in 39 patients; these patients accounted for approximately 20% of the study cohort.

At the time of diagnosis, 127 patients (62.0%) were symptomatic. We defined intestinal stenosis-related symptoms as abdominal pain or vomiting, and bleeding-related symptoms as melena and anemia secondary to tumor hemorrhage. The clinical presentation included stenosis-related symptoms in 65 (31.7%) and bleeding-related symptoms in 52 (25.4%) patients. Among patients with duodenal adenocarcinoma, 64 (43.0%) were asymptomatic at diagnosis. This is in contrast with the 47 patients (83.9%) with jejunoileal adenocarcinoma who were symptomatic at the time of diagnosis (p=0.0002). Among asymptomatic patients, 85.9% (55/64) with duodenal carcinoma were incidentally diagnosed by esophagogastroduodenoscopy (EGD), which was not specifically performed for the detection or surveillance of duodenal tumors. Five of nine (55.6%) cases of jejunoileal carcinoma were detected by computed tomography, which were performed due to abdominal surgery in four patients and a personal request in one patient.

TNM stages were as follows: 62 (41.6%), 20 (13.4%), 36 (24.2%), and 31 (20.8%) patients with stage 0/I, II, III, and IV duodenal adenocarcinoma, respectively, and 6 (10.7%), 14 (25.0%), 13 (23.2%), and 23(41.1%) with jejunoileal adenocarcinoma, respectively. Among patients with Stage IV disease, the liver and the peritoneum were the most common initial sites of metastatic disease;

liver metastasis and peritoneal metastases were present in 27 patients and lung metastases were present in 9 patients.

Overall Survival and Prognostic Factors

The median follow-up period was 26.7 months (range, 0.2-148.9). Eighty-nine patients were followed until death and 115 patients survived during the follow-up period. Figure 1 shows the complement of the Kaplan-Meier curves for TNM staging. The 3-year survival rate for Stage 0/I, II, III, and IV disease was 93.4%, 73.1%, 50.9%, and 15.1%, respectively. As the tumor stage advanced, the survival rate progressively decreased.

Table 2 shows the prognostic factors in each stage (Stage 0/I-II, Stage III, Stage IV) determined by univariate analysis. In Stage0/I-II, age (>68), ECOG PS (3-4), undifferentiated type, Hb (<12.5g/dL), Alb (<3.8g/dL), and symptomatic at diagnosis were prognostic factors for OS. In Stage III, male, NLR (≥3.0), and Plt (2.5×10^4/μl) were prognostic factors for OS. In Stage IV, age (>68), ECOG PS (3-4), CEA (>5.0mg/mL), and Alb (<3.8g/dL) were prognostic factors. Although not statistically significant, primary site of tumor (duodenum) and LDH (>240U/L) tended to be associated with a worse prognosis in Stage III.

Univariate and multivariate analyses were conducted to identify independent prognostic factors for OS; the results of these analyses are shown in Table 3. Univariate analysis revealed the following factors were significantly associated with poor OS: age >68 years, poor ECOG-PS (3-4), undifferentiated type, high CEA (>5.0ng/mL), high CA19-9 (>37U/mL), high NLR (≥3.0), high LDH (>240U/L), low Alb (<3.8g/dL), symptomatic at diagnosis, and progression of TNM Stage. Multivariate analysis showed PS 3-4 (hazard ratio [HR]: 2.26, 95% confidence interval [CI]: 1.06-4.60, p=0.035), high CEA (HR: 1.88, 95% CI: 1.09-3.22, p=0.024), high LDH (HR: 2.50, 95% CI: 1.23-4.90, p=0.012), low Alb (HR: 1.99, 95% CI:1.11-3.59, p=0.020), symptomatic (HR: 2.27, 95% CI: 1.03-5.34, p=0.042), and Stage III-IV (HR: 2.96, 95% CI: 1.52-6.16, p=0.001) were independent prognostic factors for OS.

Treatment Modality and Survival of Stage IV Patients

Among 54 patients with Stage IV disease, 25 patients (46.3%) underwent resection of the primary tumor, 33 (61.1%) received systemic chemotherapy, and 11 (20.4%) underwent local treatment for distant metastasis such as resection or radiofrequency ablation.

We defined the combined modality therapy group as patients who received all of the following: primary resection, chemotherapy, and local treatment for distant metastasis; the chemotherapy alone group was defined as those patients who received only chemotherapy for the treatment of metastatic lesions; and the best supportive care (BSC) group was defined as patients who did not receive chemotherapy.

Based on these definitions, 10 patients (18.5%) were included in the combined modality therapy group, 23 patients (43.3%) in the chemotherapy alone group, and 21 patients (38.9%) in the BSC group.

Table 4 shows the comparison of the clinical characteristics of Stage IV patients by treatment group. Kaplan-Meier curves of OS by treatment group are shown in Figure 2. The median OS for the combined modality therapy group, chemotherapy group, and BSC group was 36.9 months, 12.3 months, and 5.9 months, respectively. The OS of the combined modality therapy group was significantly longer than that of the other therapy groups (HR: 0.27, 95% CI: 0.09-0.65, p=0.0021).

Discussion

In this retrospective, multicenter, observational study, we enrolled more than 200 SBA patients at 11 institutions and investigated them in detail. Most previous studies followed a single-center retrospective design, which were likely limited by selection bias. Although there are several large-scale studies involving data from registry databases, the clinical data may have lacked sufficient detail. We expected our multicenter study to have a lower risk of selection bias than in a

single-center study and our findings likely reflect the current clinical status. We collected detailed data including data that have not been examined before. As a result, we obtained some new findings. In this study, primary SBA was most common in men in their 60s, and located in the duodenum in 72.7% of patients. The incidence of undifferentiated adenocarcinoma was 19.0%. Although the patients' characteristics in the current study were similar to previous studies [Neugut et al, 1998; Overman, 2009; Aparicio et al, 2014; Dabaja et al, 2004; Zaanan et al, 2010; Wu et al, 2006], some new knowledge was gained.

Most SBA patients are diagnosed after symptom onset. Common presenting symptoms of SBA include stenosis-related symptoms such as abdominal pain or vomiting, and bleeding-related symptoms. However, stenosis-related symptoms are rarely identified in early SBA patients, because the small intestinal products are liquid and, therefore, less likely to obstruct. As a result, most SBA patients are diagnosed with advanced disease [Dabaja et al, 2004; Talamonti et al, 2002; Halfdanarson et al, 2010; Hong et al, 2009; Chaiyasate et al, 2008]. In this study, when focusing only on duodenal adenocarcinoma, approximately 40% of patients were diagnosed with asymptomatic, early stage disease. These patients were diagnosed incidentally by screening via EGD, which is widely performed in Japan, as directed by the national health care system, for detection of gastric cancer. EGD allows for the visualization of the intestinal tract up to the 3rd portion of the duodenum. Considering the low prevalence of SBA, EGD for the detection of duodenal cancer may not be a reasonable approach. However, our findings suggest that when EGD is performed, regardless of the reason, observing the duodenum with the intention of detecting duodenal cancer is recommended. Alternatively, more than 80% of the patients with jeunoileal adenocarcinoma were symptomatic at the time of diagnosis, and most of them had progressive disease.

Crohn's disease, FAP, Lynch syndrome, Peutz-Jeghers syndrome, and celiac disease are known predisposing conditions of SBA [Gardiner & Dasari, 2007; Korelitz, 1983; Gyde et al, 1980; Ikeuchi et al, 2008; Schottenfeld et al, 2009; Giardiello et al, 2000; Swinson et al, 1983]. Recently, earlier

detection of jejunoileal cancer has been possible due to technical progress in enteroscopic techniques including video capsule endoscopy (VCE) and ballon-assisted enteroscopy (BAE). The usefulness of VCE for the detection of small bowel tumors has been reported [Cheung et al, 2010; Paquissi et al, 2015; Cheung et al, 2016]. However, in this study, there were few patients with those predisposing conditions. Given the low prevalence of SBA and the invasiveness and cost of enteroscopy, screening enteroscopy for patients without predisposing conditions is not rational. Therefore, it is crucial to identify other high-risk predisposing factors that can be easily and less invasively detected.

Previous studies have revealed that advanced age, tumor markers (CEA, CA19-9), primary site in duodenum, poorly differentiated carcinoma, pT4 tumor stage, positive resection margins, positive lymphovascular invasion, number of lymph node metastasis, resection of primary tumor, low albumin, and abnormal platelets were poor prognostic factors in SBA patients [Bilimoria et al, 2009; Dabaja et al, 2004; Zaanan et al, 2010; Talamonti et al, 2002; Halfdanarson et al, 2010; Fishman et al, 2006; Koo et al, 2011; Howe et al, 1999; Wu et al, 2006; Hong et al, 2009; Overman et al, 2008; Overman et al, 2010; Agrawal et al, 2007]. In the current study, ECOG PS 3-4, high CEA, high LDH, low albumin, symptomatic at diagnosis, and stage III-IV were found to be independent prognostic factors for OS. Our results were similar to previous studies, but our study also identified high LDH and symptomatic at diagnosis as novel prognostic factors. These factors have not been sufficiently considered in previous studies. LDH is a metabolic enzyme that catalyzes the conversion of lactate to pyruvate, and high LDH is a well-known poor prognostic factor in patients with various malignancies [Zhang et al, 2015; Li et al, 2016]. Similar to other malignancies, evaluation of serum LDH might be useful to predict prognosis in SBA patients. Given the limited number of asymptomatic patients with SBA, previous studies have not investigated the effect of the presence or absence of symptoms on disease prognosis. In our study, 69 patients (34.5%) were asymptomatic at diagnosis. Therefore, we were able to identify the presence of symptoms at diagnosis as an independent prognostic factor.

Some studies reported that duodenal carcinoma has a worse prognosis than jejunoileal carcinoma [Dabaja et al, 2004; Koo et al, 2011; Howe et al, 1999; Overman et al, 2010], and others reported that the primary site of tumor was not associated with the prognosis [Zaanan et al, 2010; Talamonti et al, 2002; Halfdanarson et al, 2010; Wu et al, 2006; Hong et al, 2009; Overman et al, 2008; Agrawal et al, 2007]. In the current study, patients with duodenal carcinoma were detected in an earlier stage compared to jejunoileal carcinoma. However, primary site was not a significant prognostic factor, which finding may have been affected by the results of Stage III patients. While not significant, there was a tendency towards worse OS in duodenal carcinoma in Stage III. One reason for this tendency may be the invasiveness of the radical resection of the duodenal carcinoma affected the result (i.e., pancreatoduodenectomy).

Univariate analysis by each stage revealed that prognostic factors (e.g., PS, Alb) in Stage 0/I-II patients related to the patient's general condition suggesting that tumor factors were not involved in the prognosis at an early stage. In Stage III, LDH (>240U/L) tended to be associated with a worse prognosis, though, there was insufficient statistical power to detect this association, because of the small number of patients. However, even without distant metastasis, LDH may be considered a prognostic factor reflecting the tumor burden when the tumor becomes a locally advanced stage.

Several studies have confirmed the survival benefit of chemotherapy for patients with advanced SBA [Dabaja et al, 2004; Zaanan et al, 2010; Halfdanarson et al, 2010; Fishman et al, 2006; Overman et al, 2008; Ouriel & Adams, 1984; Jigyasu et al, 1984; Crawley et al, 1998; Locher et al, 2005; Zaanan et al, 2011; Mizushima et al, 2013; Tsushima et al, 2012]. However, despite advances in treatment, the prognosis remains poor. Previous studies reported the OS of advanced SBA patients who received systemic chemotherapy was approximately 10-20 months [Zaanan et al, 2010; Overman et al, 2008; Locher et al, 2005; Zaanan et al, 2011; Tsushima et al, 2012]. In this study, combined modality therapy was only applicable to patients who were young, with good nutritional status, and with resectable metastatic lesions. Furthermore, the number of patients who underwent

combined modality therapy in this study was small. Therefore, it is difficult to make direct comparisons with the other treatment groups. However, the OS of 36.9 months in the combined modality therapy group was clearly long, highlighting the benefit of this treatment protocol. Some studies reported that the biological characteristics of SBA are similar to those of colorectal carcinoma [Agrawal et al, 2007; Cunningham et al, 2010; Aparicio et al, 2013], and that the chemotherapy regimen used to treat colorectal carcinoma can be applied to the treatment of SBA. In colorectal carcinoma, combined modality therapy, including resection of the liver and lung metastasis, is the standard therapy for resectable disease [Choti et al, 2002; Fong et al, 1999; Fernandez et al, 2004; Yedibela et al, 2006; Kobayashi et al, 1999; Murata et al, 1998; Ihn et al, 2017; Hernandez et al, 2016; Neeff et al, 2009; Takatsuki et al, 2016; Takahashi et al, 2013], and this approach may be appropriate for SBA. The usefulness of combined modality therapy, including local treatment of resectable metastasis, has not been assessed in previous studies. Therefore, the results of this study might help direct future research related to treatment strategies for advanced SBA.

This study has several limitations. First, this is a retrospective study; however, considering the rarity of SBA, the retrospective analysis should be acceptable. Second, patients with Lynch syndrome may be underrepresented because family history data was not collected, which likely resulted in an underestimation of patients with predisposing conditions. Third, combined modality therapy was limited to patients whose metastatic lesions were feasible for local treatment, therefore, some selection bias and institutional bias are present. However, when combined modality therapy was feasible, long-term survival was possible.

Conclusions

The results of this study suggest that when EGD is performed, regardless of the reason, observing the duodenum with the intention of detecting duodenal cancer is recommended. We found ECOG PS 3-4, high CEA, high LDH, low Alb, symptomatic at diagnosis, and stage III-IV were

independent prognostic factors for overall survival. Although the prognosis of advanced SBA was poor, combined modality therapy, including local treatment of distant metastasis, may prolong patient survival.

Ethical approval

The ethics committee of Okayama University hospital, Kurashiki Central Hospital, Okayama Saiseikai General Hospital, Hiroshima City Hiroshima Citizens Hospital, Shikoku Cancer Center, Japanese Red Cross Okayama Hospital, Kagawa Prefectural Hospital, Mitoyo General Hospital, Japanese Red Cross Society Himeji Hospital, Tsuyama Chuo Hospital, and Sumitomo Besshi Hospital approved this retrospective study and informed consent was acquired by opt-out method

Conflict of Interest

The authors declare no conflict of interest.

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Figure legends

Figure 1. Kaplan-Meier curves of overall survival by TNM stage.

Figure 2. Kaplan-Meier curves of overall survival for Stage IV patients by treatment. Combined modality therapy group refers to patients who received primary resection, chemotherapy, and local treatment for distant metastasis; the chemotherapy alone group refers to patients who received only chemotherapy; and the best supportive care (BSC) group refers to patients who did not receive chemotherapy. The OS of the combined modality therapy group was significantly longer than that of the other therapy groups (HR: 0.27, 95% CI: 0.09-0.65, p=0.0021).

Table 1. Patient characteristics

	All n=205	Duodenum n=149	Jejunoileum n=56	*p-value*
Gender, n (%)				
Male	147 (71.7)	110 (73.8)	37 (66.1)	0.28
Female	58 (28.3)	39 (26.2)	19 (33.9)	
Age, median (range)	68 (29-89)	68 (29-89)	66.5 (29-87)	0.31
Predisposing conditions, n				
None	202	149	53	
FAP	1	0	1	
Chrohn's disease	1	0	1	
Linch syndrome	1	0	1	
Histological type, n (%)				
Differentiated	163 (79.5)	117 (78.5)	46 (82.1)	0.68
Undifferentiated	39 (19.0)	30 (20.1)	9 (16.1)	
Unknown	3 (1.5)	2 (1.4)	1 (1.8)	
Symptom at diagnosis, n (%)				
Symptomatic	128 (62.4)	81 (53.7)	47 (83.9)	0.0002
Stenosis-related*	65	34	31	
Bleeding-related*	52	32	20	
Others	33	27	6	
Asymptomatic	73 (35.6)	64 (43.0)	9 (16.1)	
Unknown	4 (2.0)	4 (2.7)	0 (0.0)	
TNM Stage, n (%)				
Stage 0/I	68 (33.2)	62 (41.6)	6 (10.7)	0.0001
Stage II	34 (16.6)	20 (13.4)	14 (25.0)	
Stage III	49 (23.9)	36 (24.2)	13 (23.2)	
Stage IV	54 (26.3)	31 (20.8)	23 (41.1)	
Site of distant metastasis (Liver/ Peritoneum/ Lung/ others)	27/27/9/11	16/12/3/7	11/15/6/4	

FAP, Familial Adenomatosis Polyposis

*There is some overlapping.

Table 2. Univariate analysis for overall survival in each stage (Stage 0/I-II, Stage III, Stage IV)

	Stage 0/I/II n=102			Stage III n=49			Satge IV n=54		
	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Gender (male)	1.44	0.47-6.21	0.55	2.77	1.14-8.28	0.023	0.74	0.38-1.51	0.38
Age (>68)	3.58	1.34-11.21	0.010	1.08	0.52-2.25	0.83	2.57	1.37-4.81	0.0036
ECOG PS (3-4)	9.30	2.03-31.92	0.0072	1.67	0.49-4.35	0.38	4.85	1.82-11.79	0.0026
Primary site of tumor (Duodenum)	1.63	0.52-4.39	0.38	2.35	0.98-6.98	0.058	1.27	0.68-2.40	0.45
Histological type (Undifferentiated)	4.77	1.49-12.99	0.011	1.28	0.58-2.70	0.53	1.97	0.87-4.09	0.10
CEA (>5.0ng/ml)	1.32	0.37-3.69	0.64	1.88	0.35-34.8	0.51	2.83	1.44-5.75	0.0026
CA19-9 (>37U/ml)	1.33	0.27-23.99	0.78	2.00	0.91-4.36	0.084	1.52	0.80-2.92	0.21
NLR (≥3.0)	0.95	0.21-3.03	0.93	2.46	1.18-5.33	0.017	1.13	0.59-2.12	0.89
Hb (<12.5g/dl)	3.18	1.21-8.83	0.019	1.88	0.89-4.23	0.099	1.21	0.65-2.30	0.54
Plt (>25×10^4/μl)	1.99	0.78-5.25	0.15	2.30	1.06-5.09	0.035	0.97	0.52-1.82	0.93
ALT (>45U/L)	0.94	0.05-4.64	0.95	1.42	0.48-3.45	0.49	0.67	0.19-1.71	0.43
Cr (>1.1mg/dl)	1.98	0.46-6.08	0.32	1.30	0.21-4.53	0.73	1.65	0.56-3.89	0.33
LDH (>240U/L)	1.37	0.22-4.90	0.69	2.56	0.99-5.92	0.052	1.11	0.45-2.36	0.81
Alb (<3.8g/dl)	7.40	2.82-20.55	<0.0001	1.60	0.76-3.40	0.21	2.05	1.10-3.87	0.025
Na (<140mEq/L)	0.89	0.31-2.29	0.81	1.37	0.66-2.83	0.39	1.51	0.81-2.91	0.20
Symptoms present at diagnosis (Symptomatic)	4.40	1.59-14.01	0.004	1.31	0.54-3.93	0.58	1.08	0.46-3.15	0.88

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; Plt, platelet; ALT, alanine aminotransferase; Cr, creatinine; LDH, lactate dehydrogenase; Alb, albumin; Na, sodium

Table 3. Univariate and Multivariate analysis for overall survival

	Univariate analysis for OS			Multivariate analysis for OS		
	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Gender (male)	1.13	0.70-1.88	0.63			
Age (>68)	1.58	1.04-2.40	0.032	1.39	0.82-2.36	0.22
ECOG PS (3-4)	3.77	2.02-6.54	0.0001	2.26	1.06-4.60	0.035
Primary site of tumor (Duodenum)	1.21	0.76-1.88	0.41			
Histological type (Undifferentiated)	2.92	1.81-4.59	<0.0001	1.82	0.98-3.32	0.057
CEA (>5.0ng/ml)	2.26	1.46-3.47	0.0003	1.88	1.09-3.22	0.024
CA19-9 (>37U/ml)	2.78	1.75-4.33	<0.0001	1.59	0.90-2.78	0.11
NLR (≥3.0)	2.06	1.33-3.23	0.0011	1.04	0.60-1.78	0.89
Hb (<12.5g/dl)	2.21	1.45-3.42	0.0002	1.02	0.53-1.91	0.96
Plt (>25×10^4/μl)	1.17	0.77-1.78	0.45			
ALT (>45U/L)	1.35	0.66-2.48	0.39			
Cr (>1.1mg/dl)	1.35	0.65-2.48	0.40			
LDH (>240U/L)	1.92	1.08-3.23	0.028	2.50	1.23-4.90	0.012
Alb (<3.8g/dl)	3.33	2.8-5.10	<0.0001	1.99	1.11-3.59	0.020
Na (<140mEq/L)	1.46	0.96-2.23	0.075			
Symptoms present at diagnosis (Symptomatic)	4.15	2.47-7.42	<0.0001	2.27	1.03-5.34	0.042
Stage (III-IV)	7.21	4.37-12.53	<0.0001	2.96	1.52-6.16	0.001

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; Plt, platelet; ALT, alanine aminotransferase; Cr, creatinine; LDH, lactate dehydrogenase; Alb, albumin; Na, sodium

Table 4. Clinical characteristics of Stage IV patients by treatment group

	All n=54	Combined modality therapy n=10	Chemotherapy alone n=23	BSC n=21	*p-value*
Gender, n (%)					
Male	37 (68.5)	6 (60.0)	17 (73.9)	14 (66.7)	0.71
Female	17 (31.5)	4 (40.0)	6 (26.1)	7 (33.3)	
Age, median (range)	67.5 (29-87)	55.5 (31-73)	65 (29-83)	77 (51-87)	0.0026
ECOG PS, n (%)					
0-2	47 (87.0)	10 (100.0)	19 (82.6)	18 (85.7)	0.38
3-4	7 (13.0)	0 (0.0)	4 (17.4)	3 (14.3)	
Body mass index, median (range)	20.6 (13.8-29.7)	21.3 (19.4-26.2)	20.5 (14.7-28)	20.1 (13.8-29.7)	0.44
Primary site of tumor, n (%)					
Duodenum	32 (57.4)	6 (60.0)	14 (60.9)	11 (52.4)	0.84
Jejunum/Ileum	23 (42.6)	4 (40.0)	9 (39.1)	10 (47.6)	
Histological type, n (%)					
Differentiated	41 (77.4)	8 (80.0)	16 (72.7)	17 (80.9)	0.64
Undifferentiated	11 (20.7)	2 (20.0)	6 (27.3)	3 (14.3)	
Unknown	1 (1.9)			1 (4.8)	
Laboratory date, median (range)					
CEA (ng/ml)	5 (0.4-458)	2.9 (0.4-108.2)	4.5 (0.7-458)	6.1 (0.5-408)	0.16
CA19-9 (U/ml)	24 (0.4-6259.6)	16.95 (1-5273.6)	47.15 (3-6259.6)	15.3 (0.4-4806.8)	0.18
LDH (U/L)	177 (116-1077)	163 (145-288)	177 (116-1077)	187 (122-313)	0.77
Alb (g/dl)	3.8 (2.1-5.1)	4.2 (3.8-5.1)	4 (2.9-5.0)	3.6 (2.1-4.4)	0.036

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; Alb, albumin

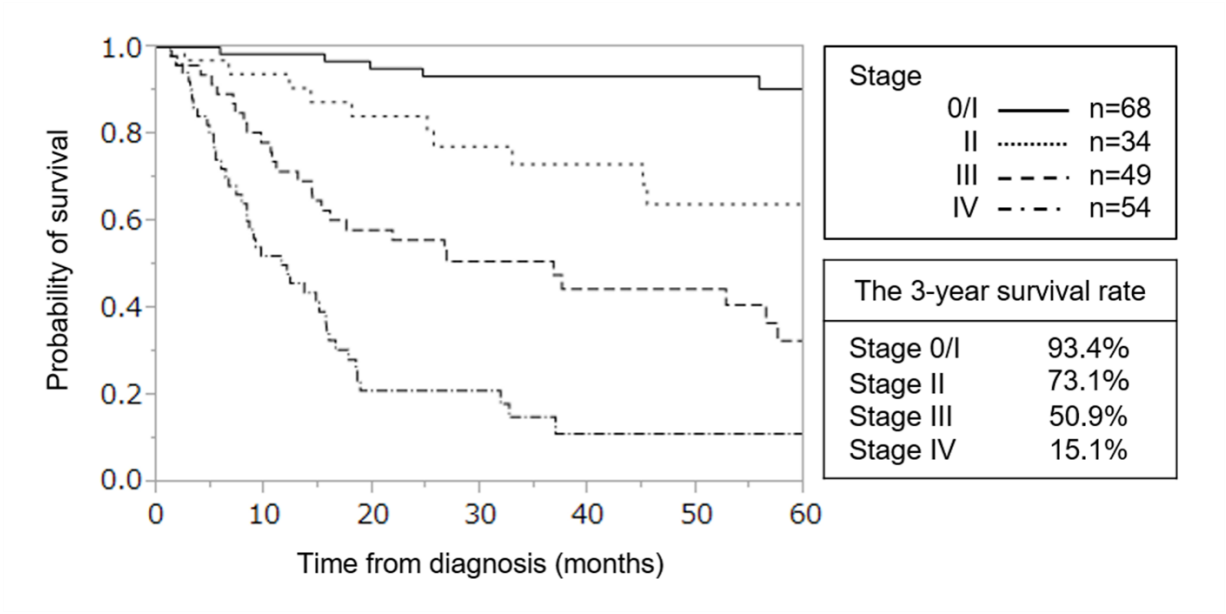
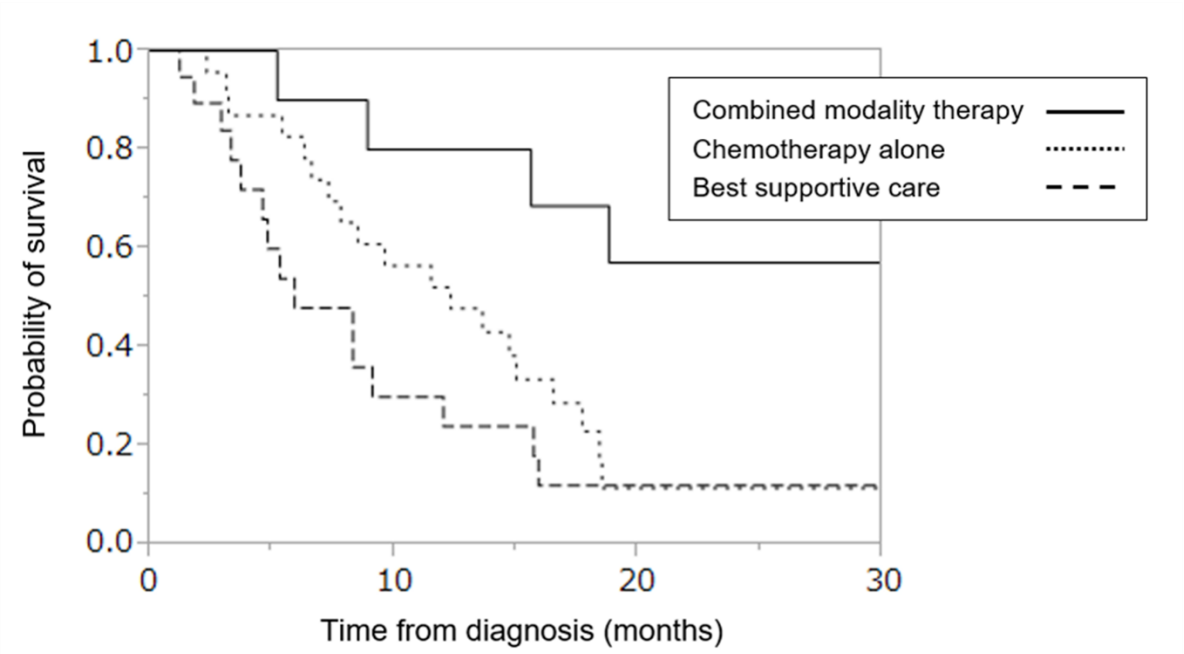


Figure 1. Kaplan-Meier curves of overall survival by TNM stage.



	n	mOS (months)
Combined modality therapy	10	36.9
Chemotherapy alone	23	12.3
Best supportive care	21	5.9

Figure 2. Kaplan-Meier curves of overall survival for Stage IV patients by treatment. Combined modality therapy group refers to patients who received primary resection, chemotherapy, and local treatment for distant metastasis; the chemotherapy alone group refers to patients who received only chemotherapy; and the best supportive care (BSC) group refers to patients who did not receive chemotherapy. The OS of the combined modality therapy group was significantly longer than that of the other therapy groups (HR: 0.27, 95% CI: 0.09-0.65, p=0.0021).