Clinical Outcomes of Small Bowel Adenocarcinoma

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Abstract

Small bowel adenocarcinomas (SBAs) are rare tumors. This study provides clinical outcomes of SBAs from the National Cancer Database. Adjuvant chemotherapy was associated with improved survival in stage II and III SBAs. Duodenal SBAs presented often with advanced stage disease, underwent surgery, adjuvant chemotherapy, and palliative chemotherapy less often, and had the worst survival. Jejunal SBAs had the best survival.

Background: Small bowel adenocarcinomas (SBAs) are rare tumors. Management of SBA is extrapolated from colorectal cancer treatments. Recent evidence suggests that the biology and molecular features of SBA differ from colorectal cancer. The aim of this study was to evaluate the management and outcome of SBA patients. **Patients and Methods:** The National Cancer Data Base (NCDB) was queried for patients with SBA between 2004 and 2013 using ICD-O-3 histology code 8140/3 and topography codes C17.0, C17.1, C17.2, C17.8, and C17.9. Univariate and multivariate survival analyses were conducted to analyze the association between SBA location and overall survival (OS) stratified by stage. Treatment outcomes of surgery, radiation, and systemic therapy were compared. **Results:** A total of 7954 SBA patients were identified; duodenum (D) 4607 (57.9%), jejunum (J) 1241 (15.6%), ileum (I) 857 (10.8%), and unspecified 1249 (15.7%). A total of 53.6% patients were male, and 76.6% white. Median age was 66 years. D mostly presented as stage IV disease (37.6%), J as stage II (34.5%) and IV disease (33.8%), and I as stage II (32.2%) and III (30.3%) disease ($P < .001$). Grade distribution was similar among D, J, and I; the majority were moderately differentiated (40.8%-55.0%), followed by poorly differentiated (30.9%-35.8%) and well differentiated (6.0%-12.4%) ($P < .001$). D underwent surgery (50.2%) less often than J (90.8%) and I (94.5%) ($P < .001$). Adjuvant radiation was provided in 8.5% of D, 2.6% of J, and 2.1% of I ($P < .001$). Adjuvant chemotherapy was provided in 21.9% of D, 50.2% of J, and 42.0% of I ($P < .001$). The rate of adjuvant chemotherapy was the highest in patients with stage III SBA, and was as follows: D (43.4%), J (65.4%), and I (63.6%) ($P < .001$). In univariate and multivariate analyses of all patients, adjuvant chemotherapy was associated with improved OS in stage II-III SBA patients. J had the best 5-year OS rate (42.0%; 95% confidence interval, 38.8-45.1, $P < .001$), and D had the worst (23.0%; 95% confidence interval, 21.6-24.2, $P < .001$). In multivariate analysis stratified by stage, chemotherapy was associated with improved OS in patients with stage II-IV SBA. **Conclusion:** Most SBA patients present with stage IV disease. D underwent surgery less often than J and I. Stage II and III D received adjuvant chemotherapy less often compared to stage II and III J and I. Adjuvant chemotherapy was associated with improved OS in patients with stage II-III disease. J had the best 5-year OS rate, and D had the worst.

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Introduction

Small bowel cancers make up 5% of all gastrointestinal malignancies, and one third of these are small bowel adenocarcinomas (SBAs).[1-3] The most common primary site of SBA is the duodenum, followed by the jejunum and ileum.[1,4] The incidence of SBAs has been on the rise in recent years, and approximately 10,000 new cases of SBA are estimated to be diagnosed in the United States annually.[5]

According to a Surveillance, Epidemiology, and End Results (SEER) cancer registry analysis from 1988 to 2007, SBAs present at an earlier age and are predominantly seen in male and African American patients compared to large bowel adenocarcinomas.[6] More than 30% of SBA patients present with high-grade stage IV disease, whereas 20% of colon cancer patients present with high-grade stage IV disease.[1,3,6] These clinical differences highlight the uniqueness of SBA and the differences between SBA and colorectal cancer.

Presenting symptoms for SBA are usually nonspecific and include abdominal pain, nausea, weight loss, fatigue, jaundice, and gastrointestinal tract bleeding.[3,4] The cause of SBAs is not well defined. Familial syndromes like Lynch syndrome, Peutz-Jeghers syndrome, and familial adenomatous polyposis, as well as chronic inflammatory conditions like Crohn disease and celiac disease, increase the risk of developing SBA.[1,3] Transformation from adenoma to dysplasia, then to carcinoma, is implicated in SBA development, similar to that seen in large bowel adenocarcinoma. Distant or nodal metastasis, T4 tumor, positive surgical margins, poorly differentiated histology, duodenal or ileal location, male sex, age $>$ 55 years, and African American ethnicity are associated with poor prognosis in SBAs.[2] Surgical treatment is used for locoregional SBAs; the type of surgery depends on the location of the SBA.[7] The role of adjuvant chemotherapy in SBAs has been debated, and prospective studies evaluating the role of adjuvant therapy in resected SBAs are lacking.[8,9]

Given the limited understanding of the etiology of SBA and the few prospective treatment trials available, we aimed to analyze the clinicopathologic features, treatment utilization patterns, and outcomes of this rare and understudied disease stratified by tumor location (duodenum, jejunum, and ileum) in the National Cancer Data Base (NCDB).

Patients and Methods

Patient Selection

The NCDB is a national clinical cancer database with data collected from over 1500 facilities that are accredited by the Commission on Cancer, which represent 70% of newly diagnosed cancers in the United States. The NCDB was queried using International Classification of Diseases for Oncology, third edition (ICD-O-3), morphology code 8140/3 and topography codes C17.0 (duodenum), C17.1 (jejunum), C17.2 (ileum), C17.8 (small intestine overlapping lesion), and C17.9 (small intestine not otherwise specified) in the participant user data file between the years 2004 and 2013.

Eligibility Criteria

Eligible patients were defined as subjects aged 18 to 90 years with stage I-IV SBA. The primary outcome was overall survival (OS) of patients with SBA based on primary tumor location. A secondary outcome was OS of stage II-III patients who received adjuvant chemotherapy. Patient-specific covariates included age at diagnosis, gender, race, histology, primary site, American Joint Committee on Cancer analytic stage group, insurance status, presence of metastatic disease, comorbid medical conditions, year of diagnosis, radiation, chemotherapy, and surgery at primary site and surgical margins, among others (Table 1). Ethical approval was not required for the study because the database is deidentified and accessible to the public.

Statistical Analysis

The clinical and demographic characteristics of the patients were summarized using descriptive statistics as appropriate for variable type and distribution. Univariate and multivariate analyses were conducted to identify factors associated with patient outcome stratified by disease stage. To assess the association between patient characteristics and survival, Cox proportional hazards models were fitted with a backward elimination method (removal criteria $P = .05$). The likelihood ratio test was used to compare the model with the covariate being assessed, both added with the model and with the assessed covariate dropped. An alpha level of .05 was used, and any covariate with likelihood ratio test $P > .05$ was removed from the final multivariate model. Kaplan-Meier curves were generated to compare OS based on tumor primary site with log-rank tests. All analyses were performed by SAS 9.4 (SAS Institute, Cary, NC) and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute in Atlanta, Georgia.

Results

Patient Demographics and Tumor Characteristics

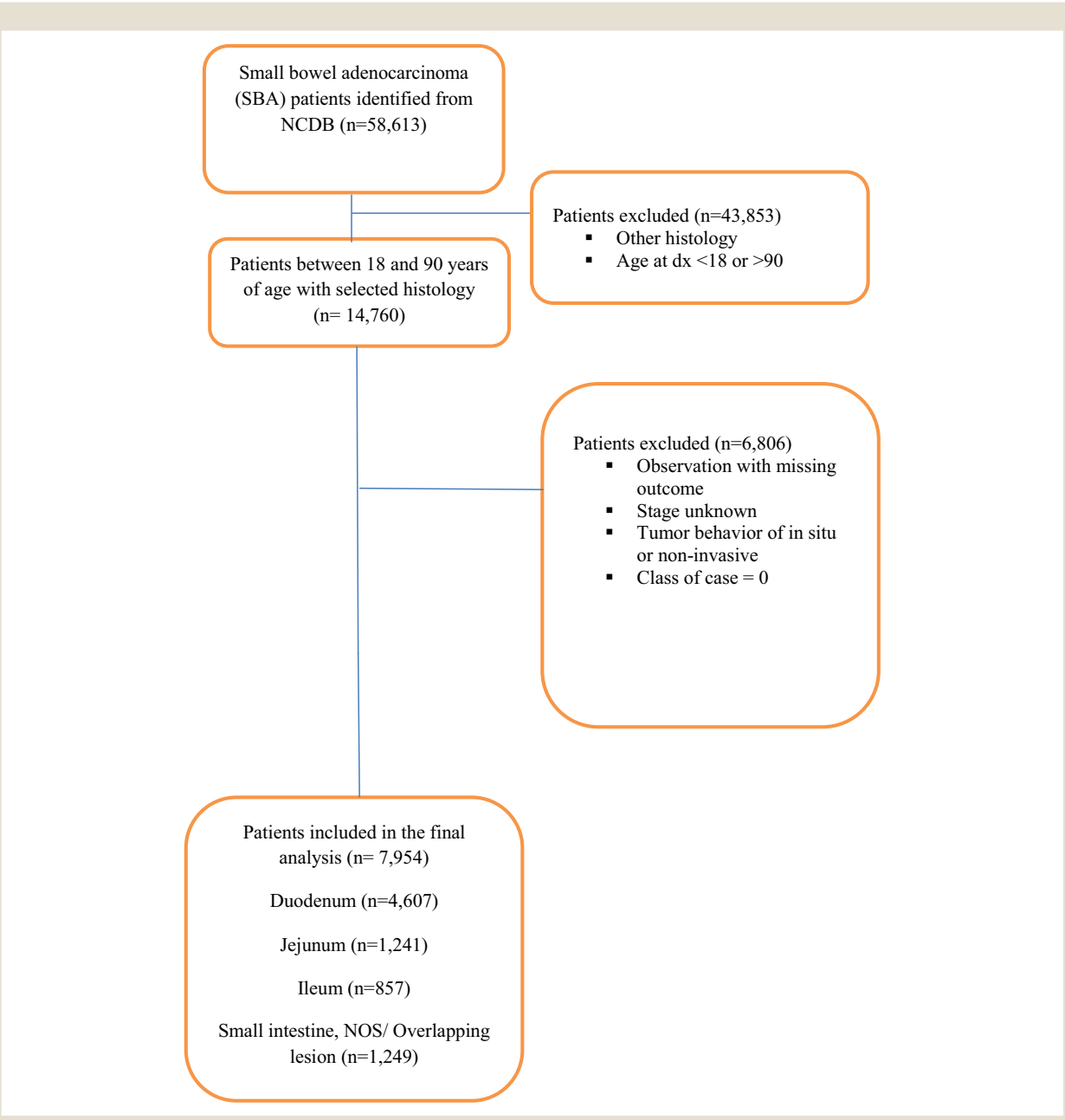
A total of 7954 patients aged between 18 and 90 years were identified, as detailed in the CONSORT diagram provided in Figure 1. Most patients (n = 4607, 57.9%) had disease located in duodenum (D) compared to jejunum (J) (n = 1241, 15.6%), ileum (I) (n = 857, 10.8%), and small intestine not otherwise specified/overlapping lesion (n = 1249, 15.7%). Patient demographics and tumor characteristics are summarized in Table 1. The median $\pm$ standard deviation age was 66 $\pm$ 14 years for the entire cohort. The median age at diagnosis was similar between all primary sites, with J presenting at a younger age and D presenting at a slightly older age (61-68 years, $P < .001$). An overall male preponderance (53.6%) was observed. This male preponderance was observed in all tumor types ($P = .397$). Whites and African Americans accounted for 76.6% and 18.9% of subjects, respectively. D, J, and I occurred more commonly in whites. Distribution across stage I to IV disease was 8.9%, 27.1%, 27.5%, and 36.4% consecutively for the entire cohort, and was significantly different among other histology groups (Table 1). D mostly presented with stage IV disease (37.6%), J with stage II (34.5%) and IV disease (33.8%), and I with stage II (32.2%) and III (30.3%) disease ($P < .001$). Grade distribution was similar among D, J, and I; the majority were moderately differentiated (40.8%-55.0%), followed by poorly differentiated (30.9%-35.8%) and well differentiated (6.0%-12.4%). Of all the tumors in the total cohort with a recorded size, the median tumor size was 40 mm, similar among all tumor locations. The percentages of patients treated at community practices and academic/research

Table 1 Baseline Demographics and Tumor Characteristics by Stage

Disease Stage	Site of Primary Tumor	No. of Patients (N = 7954)	Median Age (Years)	Male Sex	White	Lymphovascular Invasion	Poorly Differentiated/ Undifferentiated	Elevated CEA	Positive Surgical Margin	Lymph Node Positivity
Stage I	Duodenum	496	73	260 (52.4)	370 (74.6)	17 (7.14)	106 (21.37)	15 (3.0)	2 (0.4)	1 (0.2)
	Jejunum	52	65	29 (55.7)	41 (78.8)	3 (1.25)	9 (17.31)	1 (1.9)	3 (5.8)	2 (3.8)
	Ileum	93	64	44 (47.3)	83 (89.3)	3 (7.32)	10 (10.75)	4 (4.3)	2 (2.2)	0()
	Not specified	70	63	40 (57.1)	56 (80.0)	4 (11.43)	13 (18.57)	5 (7.1)	1 (1.4)	1 (1.4)
P			<.001	.608	.065	.126	.005	.129	<.001	<.001
Stage II	Duodenum	1067	68	575 (53.8)	828 (77.6)	91 (19.36)	318 (29.8)	67 (6.3)	68 (6.37)	27 (2.5)
	Jejunum	428	62.5	211 (49.3)	312 (72.9)	34 (18.09)	96 (22.43)	10 (2.3)	32 (7.5)	6 (1.4)
	Ileum	276	66	139 (50.4)	225 (81.5)	29 (22.14)	88 (31.88)	4 (1.5)	16 (5.8)	0 (0)
	Not specified	383	66	193 (50.4)	287 (74.9)	42 (25.61)	113 (29.5)	20 (5.2)	32 (8.4)	5 (1.3)
P			<.001	.326	.027	<.001	<.001	.005	<.001	<.001
Stage III	Duodenum	1310	66	747 (57)	1013 (77.3)	271 (45.32)	501 (38.24)	67 (5.1)	122 (9.3)	1103 (84.2)
	Jejunum	341	62	194 (56.9)	265 (77.7)	71 (50.35)	139 (40.76)	12 (3.5)	40 (11.7)	324 (95.0)
	Ileum	260	65	131 (50.4)	222 (85.3)	56 (52.83)	107 (41.15)	14 (5.4)	40 (15.4)	253 (97.3)
	Not specified	279	62	158 (56.6)	212 (76.0)	57 (47.11)	121 (43.37)	22 (7.9)	56 (20.1)	257 (92.1)
P			<.001	.260	.035	.418	<.001	.035	<.001	<.001
Stage IV	Duodenum	1734	68	903 (52)	1316 (75.9)	77 (9.76)	593 (34.2)	224 (12.9)	70 (4.0)	188 (10.8)
	Jejunum	420	60	225 (53.6)	278 (66.2)	70 (38.25)	140 (33.33)	59 (14.0)	115 (27.4)	185 (44.1)
	Ileum	228	62.5	123 (54.0)	201 (88.2)	50 (52.08)	102 (44.74)	37 (16.2)	68 (29.8)	126 (55.3)
	Not specified	517	61	288 (55.7)	386 (74.7)	59 (25)	172 (33.27)	75 (14.5)	118 (22.8)	169 (32.7)
P			<.001	.524	<.001	<.001	<.001	.090	<.001	<.001

Data are presented as n (%) unless otherwise indicated.
Abbreviation: CEA = carcinoembryonic antigen.

Figure 1 CONSORT Diagram Outlining Patient Selection



cancer centers were 47.2% and 41.7%, respectively. A higher number of patients were diagnosed between 2009 and 2013 (55.0%) compared to 2004-2008 (45.0%) for the entire cohort, with a similar trend seen among the different tumor locations. The majority of patients had a Charlson-Deyo score of 0 (72.3%), similar among all tumor types. Lymphovascular invasion was present mostly in the ileum (36.9%) compared to jejunum (33.2%) and duodenum (21.8%) ($P < .001$).

Treatment Modalities and Outcomes

Surgery. Surgery was performed in 66.2% of patients in the entire cohort (Table 2). Stage III patients underwent surgery the most (stage I, 69.5%; stage II, 82.2%; stage III, 88.1%; stage IV, 36.9%). Among stage III patients, those with I underwent surgery the most and D underwent surgery the least (D, 81.8%; J, 97.4%; I, 100%; $P < .001$). A similar trend was seen among stage II patients (D, 66.8%; J, 97.9%; I, 99.3%; $P < .001$), stage I patients (D, 59.1%; J, 88.5%; I, 97.9%; $P < .001$), and stage IV patients (D, 13.6%; J, 78.6%; I, 81.1%; $P < .001$). Positive surgical margins were seen in 9.9% of patients in the entire cohort, with the highest rates seen in J (15.3%) followed by I (14.7%) and D (5.7%) ($P < .001$). Positive surgical margins at pathologic evaluation were associated with worse outcomes in univariate analysis for stage II, III, and IV patients (respectively, hazard ratio [HR] = 2.24 [95% confidence interval

Table 2 Univariate Association With Primary Tumor Location by Disease Stage

Small Bowel Disease Stage and Site	No. of Patients (N = 7954)	Surgery	Chemotherapy	Single Versus Multiagent Chemotherapy	Chemotherapy After Surgery	Radiation	Radiation After Surgery	Median Follow-up (Months)
Stage I								
Duodenum	496	293 (59.1)	62 (12.5)	33 (7.1) vs. 24 (4.8)	16 (3.2)	37 (7.5)	9 (1.8)	18.3
Jejunum	52	46 (88.5)	7 (13.46)	1 (0.2) vs. 3 (0.6)	5 (9.6)	1 (1.9)	1 (0.2)	42.4
Ileum	93	91 (97.9)	3 (3.23)	1 (0.1) vs. 1 (0.1)	2 (2.1)	1 (1)	0 (0)	45.0
Not specified	70	64 (91.4)	11 (15.7)	3 (4) vs. 7 (10)	9 (12.8)	1 (1.4)	1 (0.1)	39.8
P		<.001	.032	.008	.027	.071	.622	<.001
Stage II								
Duodenum	1067	713 (66.8)	387 (36.2)	132 (12.5) vs. 222 (20.8)	199 (18.6)	221 (20.7)	117 (11.0)	19.3
Jejunum	428	419 (97.9)	164 (38.3)	42 (9.8) vs. 109 (25.4)	135 (31.5)	13 (3.0)	12 (2.8)	41.3
Ileum	276	274 (99.3)	92 (33.3)	28 (10.1) vs. 57 (20.6)	75 (27.1)	6 (2.2)	5 (1.8)	37.8
Not specified	383	364 (95.1)	123 (32.1)	28 (7.3) vs. 86 (22.4)	97 (25.3)	10 (2.6)	4 (0.1)	31.1
P		<.001	.402	.255	<.001	<.001	<.001	<.001
Stage III								
Duodenum	1310	1072 (81.8)	715 (54.6)	208 (15.9) vs. 447 (34.1)	473 (36.1)	325 (24.8)	239 (18.2)	20.5
Jejunum	341	332 (97.4)	227 (66.5)	29 (8.5) vs. 181 (5.3)	183 (53.6)	12 (3.5)	12 (3.5)	30.2
Ileum	260	260 (100)	169 (65)	29 (11.6) vs. 122 (46.9)	131 (50.3)	5 (1.9)	4 (1.5)	24.4
Not specified	279	266 (95.3)	159 (57.0)	25 (8.9) vs. 123 (44.1)	126 (45.1)	14 (5.0)	11 (3.9)	23.5
P		<.001	<.001	<.001	<.001	<.001	<.001	<.001
Stage IV								
Duodenum	1734	235 (13.5)	899 (51.8)	159 (9.2) vs. 689 (39.7)	154 (8.8)	175 (10.1)	28 (1.6)	4.9
Jejunum	420	330 (78.57)	289 (68.8)	33 (7.8) vs. 230 (54.7)	194 (46.2)	15 (3.6)	7 (1.6)	15.3
Ileum	228	185 (81.1)	135 (59.2)	18 (7.8) vs. 109 (47.8)	84 (36.8)	11 (4.8)	9 (3.9)	9.0
Not specified	517	320 (61.9)	313 (60.5)	47 (9.1) vs. 248 (47.9)	157 (30.3)	24 (4.6)	13 (2.5)	7.8
P		<.001	<.001	<.001	<.001	<.001	0.154	<.001

Data are presented as n (%) unless otherwise indicated.

Table 3 Univariate Association With Overall Survival by Disease Stage

Disease Stage	Predictor	N	HR (95% CI) *P*
Stage I	Not specified	70	0.43 (0.28-0.66) < .001
	Ileum	93	0.28 (0.18-0.43) < .001
	Jejunum	52	0.43 (0.27-0.68) < .001
	Duodenum (Ref)	496	Ref
	Well differentiated	117	0.55 (0.39-0.80) .001
	Moderately differentiated	338	0.64 (0.49-0.84) .001
	Cell type undetermined	118	1.17 (0.86-1.60) .326
	Poorly differentiated/undifferentiated (Ref)	138	Ref
	No surgery	216	7.16 (5.75-8.92) < .001
	Surgery at primary site (Ref)	494	Ref
	Age at diagnosis < 65 years	267	0.42 (0.33-0.53) < .001
	Age at diagnosis > 65 years (Ref)	444	Ref
Stage II	Not specified	383	0.76 (0.65-0.89) < .001
	Ileum	276	0.49 (0.40-0.60) < .001
	Jejunum	428	0.43 (0.36-0.51) < .001
	Duodenum (Ref)	1067	Ref
	Well differentiated	191	0.74 (0.58-0.93) .012
	Moderately differentiated	1158	0.72 (0.63-0.83) < .001
	Cell type undetermined	190	1.90 (1.56-2.32) < .001
	Poorly differentiated/undifferentiated (Ref)	615	Ref
	No surgery	383	5.76 (5.03-6.59) < .001
	Surgery at primary site (Ref)	1770	Ref
	Surgical margin positive	148	2.24 (1.81-2.78) < .001
	Surgical margin negative (Ref)	1585	Ref
	Chemotherapy	766	0.69 (0.61-0.78) < .001
	No chemotherapy (Ref)	1270	Ref
	Systemic therapy after surgery	506	0.49 (0.41-0.57) < .001
	No systemic therapy and/or no surgery (Ref)	1192	Ref
	Age at diagnosis < 65 years	964	0.47 (0.41-0.53) < .001
	Age at diagnosis > 65 years (Ref)	1190	Ref
Stage III	Not specified	279	0.86 (0.73-1.01) .072
	Ileum	260	0.85 (0.72-1.00) .056
	Jejunum	341	0.55 (0.47-0.65) < .001
	Duodenum (Ref)	1310	Ref
	Well differentiated	121	0.75 (0.58-0.95) .020
	Moderately differentiated	1042	0.76 (0.67-0.85) < .001
	Cell type undetermined	159	1.37 (1.13-1.67) .001
	Poorly differentiated/undifferentiated (Ref)	868	Ref
	No surgery	258	3.01 (2.61-3.48) < .001
	Surgery at primary site (Ref)	1930	Ref
	Surgical margin positive	258	2.05 (1.76-2.40) < .001
	Surgical margin negative (Ref)	1623	Ref
	Chemotherapy	1270	0.42 (0.38-0.47) < .001
	No chemotherapy (Ref)	803	Ref
	Systemic therapy after surgery	913	0.40 (0.35-0.45) < .001
	No systemic therapy and/or no surgery (Ref)	821	Ref
	Age at diagnosis < 65 years	1085	0.54 (0.49-0.61) < .001
	Age at diagnosis > 65 years (Ref)	1105	Ref
Stage IV	Not specified	517	0.75 (0.67-0.83) < .001
	Ileum	228	0.73 (0.63-0.85) < .001
	Jejunum	420	0.50 (0.44-0.56) < .001

Table 3 Continued

Disease Stage	Predictor	N	HR (95% CI) *P*
	Duodenum (Ref)	1734	Ref
	Well differentiated	117	0.77 (0.63-0.94) .012
	Moderately differentiated	958	0.74 (0.68-0.82) < .001
	Cell type undetermined	817	1.02 (0.92-1.12) .713
	Poorly differentiated/undifferentiated (Ref)	1007	Ref
	No surgery	1821	2.02 (1.86-2.20) < .001
	Surgery at primary site (Ref)	1070	Ref
	Surgical margin positive	371	1.42 (1.23-1.63) < .001
	Surgical margin negative (Ref)	602	Ref
	Chemotherapy	1636	0.39 (0.36-0.43) < .001
	No chemotherapy (Ref)	1178	Ref
	Systemic therapy after surgery	589	0.41 (0.37-0.45) < .001
	No systemic therapy and/or no surgery (Ref)	1759	Ref
	Age at diagnosis < 65 years	1432	0.58 (0.54-0.63) < .001
	Age at diagnosis > 65 years (Ref)	1467	Ref

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.

(CI), 1.81-2.78]; HR = 2.05 [95% CI, 1.76-2.40]; HR = 1.42 [95% CI, 1.23-1.63]; $P < .001$).

Radiation. Radiation was provided to 11.0% of patients in the entire cohort. D received the most radiation (16.5%), followed by J (3.3%) and I (2.7%) ($P < .001$). Adjuvant radiation was provided to 5.9% of patients in the entire cohort. D received the most adjuvant radiation (8.5%), followed by J (2.6%) and I (2.1%) ($P < .001$). Of patients with D, those with stage II (11.0%) and III (18.2%) disease received the most adjuvant treatment compared to stage I (1.8%) and IV (1.5%) ($P < .001$).

Chemotherapy. Chemotherapy was provided to 47.2% of patients in the entire cohort (10.3% single agent, 33.4% multiagent). J received the most chemotherapy (55.4%), followed by I (46.6%) and D (44.8%) ($P < .001$). In univariate analysis, chemotherapy was associated with improved OS compared to no chemotherapy in stage II patients (HR = 0.69; 95% CI, 0.61-0.78; $P < .001$), stage III patients (HR = 0.42; 95% CI, 0.38-0.47; $P < .001$), and stage IV patients (HR = 0.39; 95% CI, 0.36-0.43; $P < .001$) (Table 3). Similarly, in multivariate analysis, chemotherapy was associated with improved OS compared to no chemotherapy in stage II-IV patients (Table 4). Adjuvant chemotherapy was provided to 30.9% of patients in the entire cohort. J tumors received the most adjuvant chemotherapy (50.2%), followed by I tumors (42.0%) and D tumors (21.9%) ($P < .001$). Stage II disease was seen in 23.2%, 34.5%, and 32.2% of D, J, and I tumors. Of the patients with stage II disease, 18.6% of D, 31.5% of J, and 27.1% of I received adjuvant chemotherapy. Stage III was seen in 28.4%, 27.5%, and 30.3% of D, J, and I tumors, respectively. Of patients with stage III disease, 36.1% of D, 53.7% of J, and 50.3% of I received adjuvant chemotherapy ($P < .001$). In univariate analysis, adjuvant chemotherapy was associated with improved OS compared to no chemotherapy in stage II patients (HR = 0.49; 95% CI, 0.41-0.57; $P < .001$) and stage III patients (HR = 0.40; 95% CI, 0.35-0.45; $P < .001$) (Table 3). In multivariate analysis, adjuvant chemotherapy was associated with improved OS compared to no chemotherapy in stage II (HR = 0.83; 95% CI, 0.69-0.98; $P = .033$) and stage III (HR = 0.56; 95% CI, 0.49-0.64; $P < .001$) (Table 4) SBA patients.

Overall Survival

Stratified by stage, 5-year OS rate was worse for duodenal adenocarcinoma for all stages and best for jejunum adenocarcinoma for stage I-IV disease (Figure 2). In the entire patient population, median OS was 12.8 months for D (95% CI, 12.1-13.7), 40.4 months for J (95% CI, 36.1-45.6), and 34.5 months for I (95% CI, 31.2-40.2) ($P < .001$) (Figure 3). For stage II patients, median OS was 28.6 months for D (95% CI, 23.6-34.3), 99.9 months for J (95% CI, 73.8-111.2), and 99.3 months for I (95% CI, 64-NA) ($P < .001$). For stage III patients, median OS was 24.4 months for D (95% CI, 21.9-26.6), 58.6 months for J (95% CI, 41.4-94.9), and 33.1 months for I (95% CI, 25.3-41.8) ($P < .001$). Stage IV disease was seen in 37.6%, 33.8%, and 26.6% of D, J, and I tumors ($P < .001$); median OS was 5.1 (95% CI, 4.7-5.7), 16.1 (95% CI, 14.6-19.8), and 9.7 (95% CI, 7.2-13.4) months, respectively ($P < .001$).

In multivariate analysis of stage II patients with SBA, primary tumor location in J (HR = 0.65; 95% CI, 0.54-0.78; $P < .001$), treatment at academic/research program (HR = 0.75; 95% CI, 0.65-0.86; $P < .001$), well/moderately differentiated histology (HR = 0.67; 95% CI, 0.52-0.85; $P = .001$/HR = 0.72; 95% CI, 0.63-0.83; $P < .001$), surgery at primary site, radiation, chemotherapy (HR = 0.60; 95% CI, 0.49-0.73; $P < .001$), and age at diagnosis < 65 years (HR = 0.62; 95% CI, 0.54-0.71; $P < .001$) were associated with better OS compared to primary tumor location in D, treatment at comprehensive community program, poorly differentiated histology, no surgery (HR = 5.59; 95% CI, 4.71-6.63; $P < .001$), no radiation (HR = 1.30; 95% CI, 1.07-1.59; $P = .008$), no chemotherapy, and age at diagnosis > 65 years. In multivariate analysis of stage III patients with SBA, primary tumor location in J (HR = 0.70; 95% CI, 0.58-0.83; $P < .001$), year of diagnosis between 2009 and 2013 (HR = 0.89;

Table 4 Multivariate Association With Overall Survival by Disease Stage

Disease Stage	Predictor	HR (95% CI) *P*	Type 3 *P*
Stage I	Not specified	0.67 (0.42-1.05) .081	<.001
	Ileum	0.44 (0.27-0.69) < .001	
	Jejunum	0.51 (0.31-0.81) .005	
	Duodenum (Ref)	Ref	
	Community cancer program	1.14 (0.82-1.59) .446	.050
	Academic/research program	0.74 (0.57-0.94) .016	
	Integrated network cancer program	0.93 (0.64-1.37) .719	
	Other types of cancer programs	0.58 (0.23-1.44) .237	
	Comprehensive community cancer program (Ref)	Ref	
	No surgery	6.54 (5.11-8.38) < .001	<.001
	Surgery at primary site (Ref)	Ref	
	No radiation	1.86 (1.14-3.04) .013	<.001
	Radiation (Ref)	Ref	
	Chemotherapy	0.62 (0.38-1.02) .058	.008
	No chemotherapy (Ref)	Ref	
Stage II	Not specified	1.05 (0.88-1.25) .593	<.001
	Ileum	0.70 (0.56-0.87) .001	
	Jejunum	0.65 (0.54-0.78) < .001	
	Duodenum (Ref)	Ref	
	Community cancer program	1.22 (0.99-1.50) .065	<.001
	Academic/research program	0.75 (0.65-0.86) < .001	
	Integrated network cancer program	0.95 (0.78-1.16) .637	
	Other types of cancer programs	0.46 (0.29-0.72) < .001	
	Comprehensive community cancer program (Ref)	Ref	
	Well differentiated	0.67 (0.52-0.85) .001	<.001
	Moderately differentiated	0.72 (0.63-0.83) < .001	
	Cell type undetermined	0.81 (0.65-1.00) .055	
	Poorly differentiated/undifferentiated (Ref)	Ref	
	No surgery	5.59 (4.71-6.63) < .001	<.001
	Surgery at primary site (Ref)	Ref	
	No radiation	1.30 (1.07-1.59) .008	.009
	Radiation (Ref)	Ref	
	Chemotherapy	0.60 (0.49-0.73) < .001	<.001
	No chemotherapy (Ref)	Ref	
	Systemic therapy after surgery	0.83 (0.69-0.98) .033	.331
	No systemic therapy and/or no surgery (Ref)	Ref	
	Age at diagnosis < 65 years	0.62 (0.54-0.71) < .001	<.001
	Age at diagnosis > 65 years (Ref)	Ref	
Stage III	Not specified	1.00 (0.84-1.19) .992	<.001
	Ileum	1.09 (0.91-1.30) .344	
	Jejunum	0.70 (0.58-0.83) < .001	
	Duodenum (Ref)	Ref	
	Year of diagnosis 2009-2013	0.89 (0.80-1.00) .043	.043
	Year of diagnosis 2004-2008 (Ref)	Ref	
	Well differentiated	0.70 (0.55-0.90) .005	<.001
	Moderately differentiated	0.76 (0.68-0.86) < .001	
	Cell type undetermined	0.68 (0.54-0.84) < .001	
	Poorly differentiated/undifferentiated (Ref)	Ref	
	No surgery	2.96 (2.50-3.51) < .0001	<.001
	Surgery at primary site (Ref)	Ref	
	Chemotherapy	0.47 (0.39-0.57) < .001	<.001
	No chemotherapy (Ref)	Ref	

Table 4 Continued

Disease Stage	Predictor	HR (95% CI) *P*	Type 3 *P*
	Systemic therapy after surgery	0.56 (0.49-0.64) < .001	<.001
	No systemic therapy and/or no surgery (Ref)	Ref	
	Age at diagnosis < 65 years	0.68 (0.61-0.76) < .001	<.001
	Age at diagnosis > 65 years (Ref)	Ref	
Stage IV	Not specified	1.07 (0.95-1.20) .283	.055
	Ileum	1.08 (0.92-1.27) .338	
	Jejunum	0.89 (0.77-1.02) .100	
	Duodenum (Ref)	Ref	
	Other/unknown	0.82 (0.66-1.01) .063	<.001
	African American	0.83 (0.74-0.92) < .001	
	White (Ref)	Ref	
	Community cancer program	1.15 (1.00-1.32) .044	<.001
	Academic/research program	0.81 (0.74-0.89) < .001	
	Integrated network cancer program	0.99 (0.87-1.13) .868	
	Other types of cancer programs	0.72 (0.58-0.90) .003	
	Comprehensive community cancer program (Ref)	Ref	
	Year of diagnosis 2009-2013	1.10 (1.02-1.20) .016	.016
	Year of diagnosis 2004-2008 (Ref)	Ref	
	Well differentiated	0.72 (0.58-0.89) .002	<.001
	Moderately differentiated	0.76 (0.69-0.84) < .001	
	Cell type undetermined	0.77 (0.70-0.85) < .001	
	Poorly differentiated/undifferentiated (Ref)	Ref	
	No surgery	1.94 (1.74-2.17) < .001	<.001
	Surgery at primary site (Ref)	Ref	
	No radiation	1.00 (0.86-1.15) .967	.004
	Radiation (Ref)	Ref	
	Chemotherapy	0.42 (0.38-0.46) < .001	<.001
	No chemotherapy (Ref)	Ref	
	Age at diagnosis < 65 years	0.84 (0.74-0.95) .007	.007
	Age at diagnosis > 65 years (Ref)	Ref	

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.

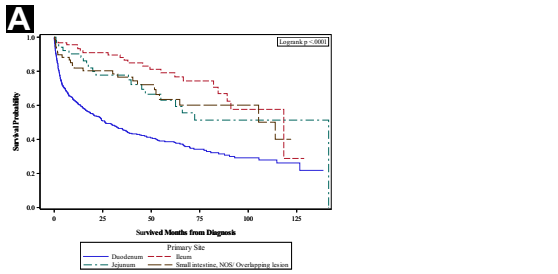
95% CI, 0.80-1.00; $P = .043$), well/moderately differentiated histology (HR = 0.70; 95% CI, 0.55-0.90; $P = .005$/HR = 0.76; 95% CI, 0.68-0.86; $P < .001$), surgery, chemotherapy (HR = 0.47; 95% CI, 0.39-0.57; $P < .001$), and age at diagnosis < 65 years (HR = 0.68; 95% CI, 0.61-0.76; $P < .001$) were associated with better OS compared to primary tumor location in D, year of diagnosis between 2004 and 2008, poorly differentiated histology, no surgery (HR = 2.96; 95% CI, 2.50-3.51; $P < .001$), no chemotherapy, and age at diagnosis > 65 years. In multivariate analysis of stage IV patients with SBA, African American race (HR = 0.83; 95% CI, 0.74-0.92; $P < .001$), treatment at academic/research program (HR = 0.81; 95% CI, 0.74-0.89; $P < .001$), well/moderately differentiated histology (HR = 0.72; 95% CI, 0.58-0.89; $P = .002$; HR = 0.76; 95% CI, 0.69-0.84; $P < .001$), surgery, chemotherapy (HR = 0.42; 95% CI, 0.38-0.46; $P < .001$), and age at diagnosis < 65 years (HR = 0.84; 95% CI, 0.74-0.95; $P = .007$) were associated with better OS compared to white race, treatment at comprehensive community program, poorly differentiated histology, no surgery (HR = 1.94; 95% CI, 1.74-2.17; $P < .001$), no chemotherapy, and age at diagnosis > 65 years (Table 4).

Discussion

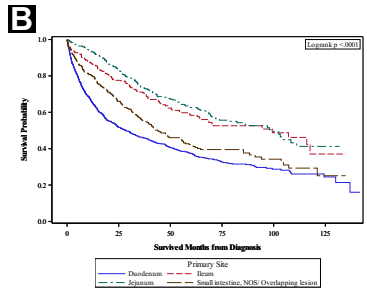
SBAs are rare tumors and have unique clinical presentations, treatment strategies, and outcomes compared to large bowel adenocarcinomas. This NCDB analysis aimed to improve the current understanding of the epidemiology, clinical presentation, pathologic features, multimodal treatment utilization, and OS of SBA based on tumor location. The patient demographics in this study are consistent with prior population-based studies.[6] However, the current study additionally reports the patterns of chemotherapy utilization (single vs. multiagent, adjuvant vs. palliative) and provides outcome data specific to SBA location.

In this study, duodenal adenocarcinomas presented with more stage III and IV disease compared to other sites. Despite having a worse prognosis in all stages, patients with stage II and III duodenal adenocarcinoma were administered less adjuvant chemotherapy compared to same-stage jejunum and ileum adenocarcinomas. The reason for underutilization of adjuvant chemotherapy in duodenal adenocarcinoma is unclear. The role of adjuvant chemotherapy in SBAs has long been debated, and prospective studies evaluating the role of adjuvant therapy in resected SBAs are lacking.[8,9] Retrospective studies reported mixed results in the adjuvant setting.[4,9]

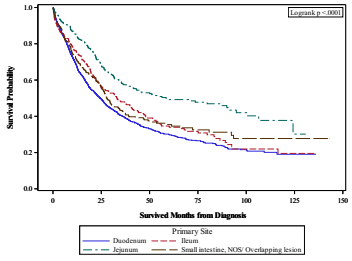
Figure 2 Survival Curves by Disease Stage and Tumor Location. (A) Stage I Survival Curve by Tumor Location. (B) Stage II Survival Curve by Tumor Location. (C) Stage III Survival Curve by Tumor Location. (D) Stage IV Survival Curve by Tumor Location



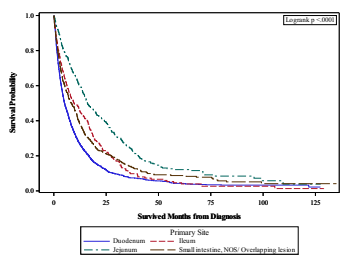
Primary Site	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Duodenum	496	296 (60%)	200 (40%)	26.3 (20.3, 35.9)	61.5% (57.0%, 65.6%)	38.7% (33.9%, 43.4%)
Ileum	93	22 (24%)	71 (76%)	118.3 (89.2, NA)	94.4% (87.1%, 97.6%)	79.1% (67.2%, 87.1%)
Jejunum	52	20 (38%)	32 (62%)	141.5 (55, 141.5)	90.2% (78.0%, 95.8%)	63.0% (46.1%, 75.9%)
Small intestine, NOS/ Overlapping lesion	70	23 (33%)	47 (67%)	113.9 (54.2, NA)	81.9% (70.3%, 89.3%)	63.5% (48.1%, 75.3%)



Primary Site	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Duodenum	1067	640 (60%)	427 (40%)	28.6 (23.6, 34.3)	65.5% (62.6%, 68.3%)	37.4% (34.1%, 40.7%)
Ileum	276	107 (39%)	169 (61%)	99.3 (64, NA)	86.7% (82.1%, 90.3%)	58.3% (51.3%, 64.7%)
Jejunum	428	155 (36%)	273 (64%)	99.9 (73.8, 111.2)	93.3% (90.4%, 95.3%)	62.6% (57.1%, 67.7%)
Small intestine, NOS/ Overlapping lesion	383	204 (53%)	179 (47%)	43.8 (36.6, 55.8)	80.1% (75.8%, 83.8%)	42.2% (36.5%, 47.9%)



Primary Site	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Duodenum	1310	868 (66%)	442 (34%)	24.4 (21.9, 26.6)	68.4% (65.8%, 70.9%)	29.9% (27.1%, 32.7%)
Ileum	260	164 (63%)	96 (37%)	33.1 (25.3, 41.8)	76.2% (70.5%, 81.0%)	34.6% (28.1%, 41.2%)
Jejunum	341	159 (47%)	182 (53%)	58.6 (41.4, 94.9)	84.8% (80.5%, 88.2%)	49.2% (43.1%, 55.1%)
Small intestine, NOS/ Overlapping lesion	279	165 (59%)	114 (41%)	27.9 (24.9, 34.5)	71.8% (66.1%, 76.8%)	35.4% (29.1%, 41.8%)

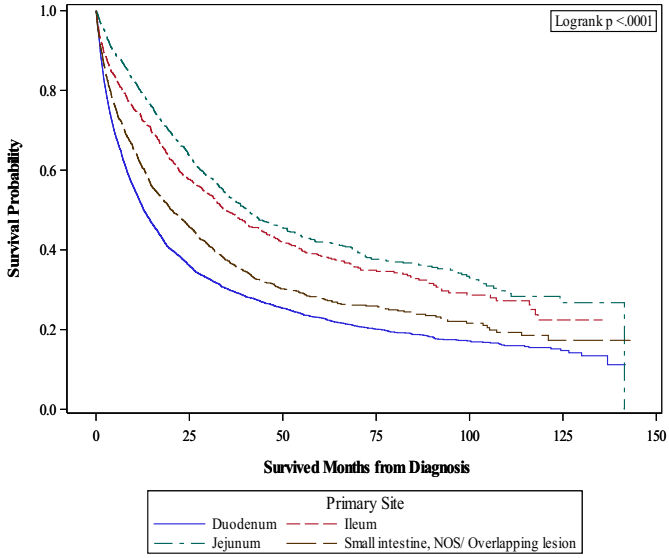


Primary Site	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Duodenum	1734	1585 (91%)	149 (9%)	5.1 (4.7, 5.7)	27.5% (25.4%, 29.7%)	4.3% (3.2%, 5.6%)
Ileum	228	207 (91%)	21 (9%)	9.7 (7.2, 13.4)	46.7% (40.0%, 53.0%)	4.6% (2.2%, 8.6%)
Jejunum	420	338 (80%)	82 (20%)	16.1 (14.6, 19.8)	60.4% (55.5%, 65.0%)	12.1% (8.7%, 16.1%)
Small intestine, NOS/ Overlapping lesion	517	454 (88%)	63 (12%)	8.3 (6.8, 10.1)	39.4% (35.2%, 43.7%)	8.7% (6.2%, 11.9%)

Utilization of adjuvant chemotherapy has increased in recent years.[2] In this study, adjuvant chemotherapy was associated with improved OS compared to no chemotherapy in both univariate and multivariate analyses of all SBA patients with stage II and III disease. Ecker et al[10] reported superior median OS in stage III SBA patients treated with adjuvant chemotherapy compared to surgery alone in their NCDB analysis, whereas no statistically significant median OS benefit was shown in stage I and II disease in the entire cohort. There was survival benefit of adjuvant chemotherapy in stage III duodenal and jejunoileal tumors when a separate subset analysis was performed on the basis of tumor location. No survival benefit was observed in stage II patients irrespective of tumor location. A standard chemotherapy regimen was not established in the adjuvant setting. 5-FU/LV (5-fluorouracil/leucovorin), FOLFOX (folinic acid, fluorouracil, and oxaliplatin), FOLFIRI (5-fluorouracil, leucovorin and irinotecan), and 5-fluorouracil/cisplatin regimens were used in retrospective studies with no difference in outcomes between regimens.[11,12] There is an ongoing phase 3 clinical trial evaluating the role of adjuvant chemotherapy (observation vs. single agent 5-fluorouracil vs. FOLFOX in resected SBAs, which will answer this question in a prospective setting (NCT02502370).

In this study, duodenal adenocarcinoma had the worst median OS and 5-year OS rate compared to jejunum and ileum adenocarcinomas at all stages. The prognosis of SBAs varies significantly by tumor location despite following a similar adenoma-to-carcinoma transformation, as in colorectal adenocarcinoma. Duodenal location is associated with poor prognosis in SBA, and the site of the tumor has therapeutic implications in the management of SBAs. Although duodenal adenocarcinoma could be managed by pancreaticoduodenectomy or wide local excision with regional lymphadenectomy, jejunal and ileal adenocarcinomas are typically managed by wide local excision and regional lymph node excision.[1,3] Among this study's entire cohort, stage IV SBA patients with duodenal adenocarcinoma had the poorest median OS; however, systemic chemotherapy utilization was the lowest in this group compared to other locations. Single-agent chemotherapy was administered to 9.2% of stage IV duodenal adenocarcinoma, and multiagent chemotherapy was administered to 39.7% of these patients ($P < .001$). Multivariate analysis of stage IV patients revealed improved OS of patients who received chemotherapy compared to those who did not.

Figure 3 Survival by Tumor Location for All Disease Stages Combined



Primary Site	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Duodenum	4607	3389 (74%)	1218 (26%)	12.8 (12.1, 13.7)	51.6% (50.2%, 53.1%)	23.0% (21.6%, 24.3%)
Ileum	857	500 (58%)	357 (42%)	34.5 (31.2, 40.2)	73.6% (70.5%, 76.5%)	38.6% (34.9%, 42.3%)
Jejunum	1241	672 (54%)	569 (46%)	40.4 (36.1, 45.6)	79.7% (77.3%, 81.8%)	42.0% (38.8%, 45.1%)
Small intestine, NOS/ Overlapping lesion	1249	846 (68%)	403 (32%)	20.1 (17.8, 23.7)	61.4% (58.6%, 64.1%)	27.9% (25.2%, 30.8%)

In the metastatic disease setting, palliative chemotherapy is the mainstay of treatment, although the data are based on retrospective studies and prospective phase 2 studies.[3,13] A combined analysis from 6 retrospective studies showed a median OS of SBA of 13 months for patients receiving systemic chemotherapy, compared to 4 months for those treated with best supportive care alone.[1,4,14-18] Modified FOLFOX and CAPOX (capecitabine and oxaliplatin) chemotherapy regimens resulted in a median OS of 15.2 and 20.4 months, respectively, in phase 2 trials; thus, frontline therapy for SBA could consist of either CAPOX or FOLFOX.[19,20] Different chemotherapeutic regimens have also been explored in retrospective studies and phase 2 trials. For example, in a phase 2 study of a combination of first-line capecitabine, irinotecan, and oxaliplatin in 33 patients with advanced SBA, a confirmed response rate of 37.5% and a median OS of 13.4% were reported.[21] A retrospective multicenter study of 93 patients with advanced SBA reported median OS values of 13.5, 17.8, 10.6, and 9.3 months with first-line 5-FU/LV, FOLFOX, FOLFIRI, and 5-fluorouracil, leucovorin, and cisplatin chemotherapy regimens, respectively.[13] Objective response rates were 0%, 34%, 9%, and 31%, respectively. A single-center retrospective study of 113 patients reported a 41% overall response rate in patients with gemcitabine-containing regimens and a 41.6% rate in irinotecan-containing regimens.[14] Single-agent nab-paclitaxel resulted in a 20% objective response rate in 10 patients with advanced SBA in a phase 2 study in the setting of treatment-refractory disease.[22] First-line CAPOX plus bevacizumab was studied in a single-arm phase 2 study of 30 patients with SBA and found an overall response rate of 48.3% and a median OS of 12.9 months.[23] Clinical efficacy with the anti-EGFR inhibitors panitumumab and cetuximab as a single agent or in combination with FOLFOX or FOLFIRI regimens was described in a case series and in retrospective studies, with various success rates.[24-26] However, no objective response was seen in a single-arm phase 2 study of 9 patients with treatment-refractory 9 *RAS* wild-type metastatic SBA and ampullary adenocarcinoma.[27]

Limitations of this study include its retrospective design and the absence of detailed information on the chemotherapy regimens in the NCDB. In addition, disease-specific mortality, recurrence indexes, response to treatment, and history of malignancies are not captured in the NCDB. Furthermore, specific radiation and surgical treatments utilized in this cohort of patients could not be determined. Despite these limitations, the strengths of this study are that NCDB data may provide a better understanding of the surgical outcomes and of receipt of chemotherapy in the adjuvant or palliative setting, and could provide guidance for treatment decisions for these rare tumors.

Conclusion

Most SBA patients present with stage IV disease. D underwent surgery less often than J and I. Stage II and III D received adjuvant

chemotherapy less often compared to stage II and III J and I. Adjuvant chemotherapy was associated with improved OS in stage II-III patients. J had the best 5-year OS rate, and D the worst.

Clinical Practice Points

- Patients with duodenal SBA presented with more advanced disease but were administered palliative chemotherapy less often.
- Patients with stage II-III duodenal SBA underwent surgery and received adjuvant chemotherapy less often than patients with jejunal and ileal SBA.
- Adjuvant chemotherapy was associated with improved OS in patients with stage II-III SBA.
- Duodenal SBA had the worst OS and 5-year survival at all disease stages.
- Jejunal SBA had the best median OS and 5-year survival for at all disease stages.

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Disclosure

The authors have stated that they have no conflict of interest.

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