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Novel Prognostic Factors in Resected Small Bowel Adenocarcinoma

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Abstract

Small bowel adenocarcinoma is a rare malignancy with variable survival depending on multiple factors. Increased age, increased tumor stage, and low lymphocyte-to-monocyte ratio before surgery are associated with poor overall survival. Patients with stage III disease showed improved survival when provided adjuvant chemotherapy.

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy affecting approximately 3000 patients per year in the United States, and there is limited evidence prognosticating patients with resected SBA. We aimed to evaluate prognostic factors and the role of adjuvant therapy in patients with resected SBA. **Patients and Methods:** Two hundred forty-one patients who had resected stage I-III SBA were retrospectively identified at a single tertiary referral institution. Overall survival (OS) analysis was performed by the Kaplan-Meier method, and Wilcoxon tests were used for statistical comparisons. Cox proportional hazards were performed to identify significant variables by univariate and multivariate analysis. **Results:** Median OS for the entire group was 54.5 months (95% confidence interval [CI], 37.2-81.2 months), with 5- and 10-year OS of 48% and 35%. Median follow-up was 113.7 months (95% CI, 97.9-126.6 months). For patients with stage III disease who received adjuvant therapy, the median OS was 33.8 months (95% CI, 27.8-78.8) compared to 24.7 months (95% CI, 11.5-37.8) for patients with no adjuvant therapy ($P < .01$). Male sex, advanced T stage, advanced N stage, increased positive lymph node ratio, lymphocyte-to-monocyte ratio < 1.56, presence of residual disease, and earlier date of diagnosis predicted worse survival on univariate analysis. Age > 60 years, lymphocyte-to-monocyte ratio < 1.56, and advanced T stage were identified as independent negative predictors of OS for all patients by multivariate analysis. **Conclusion:** Advanced age, advanced T stage, and lymphocyte-to-monocyte ratio < 1.56 independently predicted survival in resected SBA. Adjuvant therapy is associated with improved survival in patients with resected stage III SBA.

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Introduction

Small intestinal cancers account for 3.3% of all newly identified malignancies of the digestive system and less than 1% of all malignancies each year.[1] Over the last 30 years, small bowel adenocarcinoma (SBA) has become the second most common primary small bowel malignancy, recently being surpassed by carcinoid tumors.[2,3] Surgical resection of the primary tumor has been established as the most effective treatment modality.[3-5]

At present, there are no large prospective randomized trials supporting the delivery of adjuvant chemotherapy in resectable SBA. One prospective trial that included periampullary tumors seemed to suggest a survival benefit with adjuvant chemotherapy, though the sample size was small.[6] In a retrospective analysis of 54 patients, adjuvant therapy was associated with improved disease-free survival, but not overall survival (OS). There were data suggesting survival benefit with adjuvant therapy in patients with 10% positive lymph nodes.[7] A review of a large cohort of patients suggested that adjuvant chemotherapy may improve survival in patients with stage

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Table 1 Patient Characteristics

Characteristic	All Patients (N = 241)	No Adjuvant Therapy (N = 156)	Adjuvant Therapy (N = 85)	*P* Interaction[a]
Age (y), median (range)	65 (25-92)	68 (25-92)	57 (31-85)	<.01
Male sex	151 (63)	98 (62)	53 (62)	1
Year of Diagnosis				
1994-2006	149 (62)	97 (62)	52 (61)	1
2006-2017	92 (38)	59 (38)	33 (39)	
Primary Site of Tumor				
Duodenum	156 (65)	104 (67)	52 (61)	.06
Jejunum	56 (23)	34 (22)	22 (26)	
Ileum	22 (9)	16 (10)	6 (7)	
NOS	7 (3)	2 (1)	5 (6)	
Grade				
1	3 (1)	3 (2)	0 (0)	.05
2	68 (29)	51 (33)	17 (20)	
3	140 (59)	85 (54)	55 (65)	
4	26 (11)	13 (8)	13 (15)	
T Stage				
1	19 (8)	16 (10)	3 (4)	.05
2	22 (9)	17 (11)	5 (6)	
3	111 (48)	67 (43)	44 (52)	
4	81 (35)	49 (31)	32 (38)	
N Stage				
0	113 (50)	85 (59)	28 (34)	<.01
1	78 (35)	44 (31)	34 (41)	
2	35 (15)	14 (10)	21 (25)	
Surgical Margin				
R0	221 (92)	138 (88)	83 (98)	.05
R1	18 (8)	16 (10)	2 (2)	
Overall Stage				
I	34 (15)	30 (19)	4 (5)	<.01
II	92 (41)	67 (43)	25 (29)	
III	100 (44)	45 (29)	56 (67)	

Data are presented as n (%) unless otherwise indicated.
Abbreviation: NOS = not otherwise specified.
[a]Tests performed included Fisher exact test for binary categorical variables, Pearson for multiple categorical variables, and *t* test for continuous variables.

III disease; however, specific regimens were not identified, given the nature of the database.[5] Systemic fluoropyrimidine-based chemotherapy (5-fluorouracil [5-FU] alone or in combination with oxaliplatin [FOLFOX]) has demonstrated survival benefit in metastatic SBA.[8] Other regimens have been evaluated as well, such as capecitabine, irinotecan, and oxaliplatin (CAPIRINOX) and 5-FU, doxorubicin, and mitomycin C (FAM).[9,10] Use of adjuvant therapy in SBA has been extrapolated from colorectal adenocarcinoma data, and therefore its use has increased over the last 30 years, particularly in patients with high-risk disease.[3,11,12]

Many prognostic markers have been evaluated in SBA. Histopathologic features such as positive surgical margins, extramural venous invasion, positive lymph nodes, tumor differentiation, and depth of tumor invasion may have prognostic significance.[13] Other studies have suggested age, race, nodal metastases, T stage, tumor grade, resection, and use of systemic therapy to be independent predictors of survival.[3,14,15] In patients receiving adjuvant chemotherapy, lymph node positivity and total number of lymph nodes removed during surgery have been shown to have prognostic significance.[15] Peripheral blood counts have been associated with survival in hematologic and solid tumor malignancies, though there are few data in SBA.[16-18]

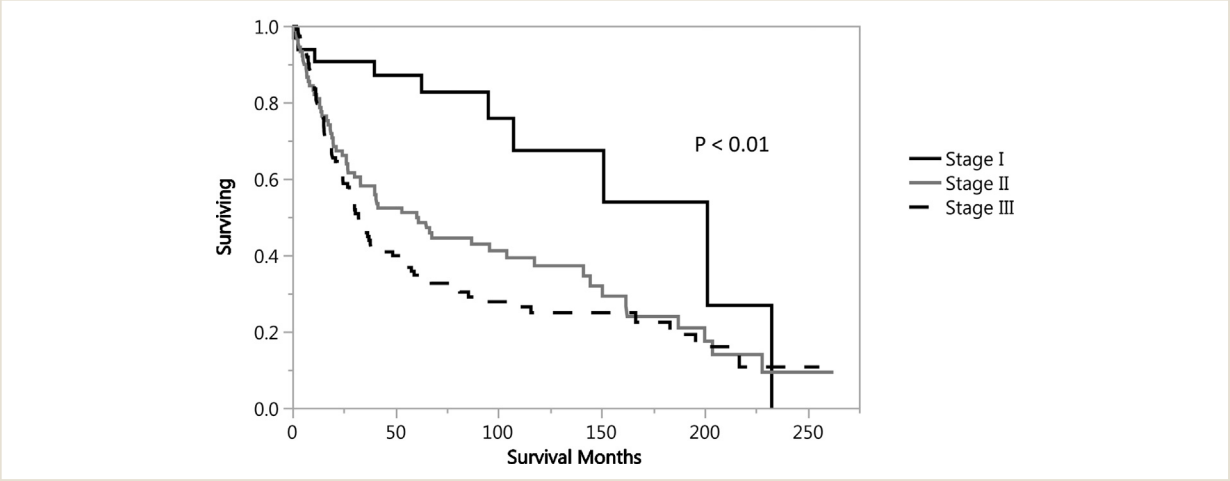
In this study, we studied prognostic factors and updated survival outcomes in patients with early stage SBA (stages I-III) treated at Mayo Clinic over 22 years.

Patients and Methods

Patient Selection

Patients who had SBA diagnosed between January 1994 and January 2016 were identified through the Mayo Clinic patient record registry. Data on patients diagnosed between 1994 and 2006 were previously collected and reported.[19] We updated the OS for

Figure 1 Kaplan-Meier Survival Curves Demonstrating OS in Patients With Stage I-III Disease. Median OS for all Stage I Disease was 201 Months (95% CI, 107-232), Stage II Disease 61 Months (95% CI, 33-117), and Stage III Disease was 32 Months (95% CI, 24.5-49)



Abbreviations: CI = confidence interval; OS = overall survival.

the entire cohort and collected additional information on peripheral blood cell counts. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer guidelines.[20] The study was approved by the Mayo Clinic institutional review board.

Data Collection

We collected available information about chemotherapy, and patients were listed as having received adjuvant therapy if the medical record indicated that such therapy was provided. We excluded patients with ampullary cancer and patients with metachronous cancers to describe survival in SBA alone. The date of death was obtained from Mayo Clinic records, and it was supplemented with publicly available death indexes and Internet searches for obituaries corroborating at least 2 patient identifiers (date of birth and name). Preoperative peripheral differential blood counts within 1 month of the date of surgery were recorded to calculate the lymphocyte-to-monocyte ratio (LMR).

Statistical Analysis

OS was performed by the Kaplan-Meier method, and Wilcoxon tests were used for statistical comparisons. The optimal cutoff value for LMR was determined using a receiver operator characteristic curve and the Youden index on the binary outcome of dead/alive at the last known follow-up.[21] A training set for LMR included consecutively identified patients from 2006 to 2015, and a validation cohort including patients identified from 1994 to 2005 was used. Multivariate Cox proportional hazard models were performed to control for age, sex, T stage, N stage, lymph node ratio, tumor location, LMR, margin status, adjuvant therapy, and date of diagnosis. All tests were 2 sided, and $P < .05$ was considered significant. JMP Pro 13.0.0 software (SAS Institute, Cary, NC) was used for statistical analysis. R software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/) was used for establishing optimal cutoff value.

Results

Basic Characteristics

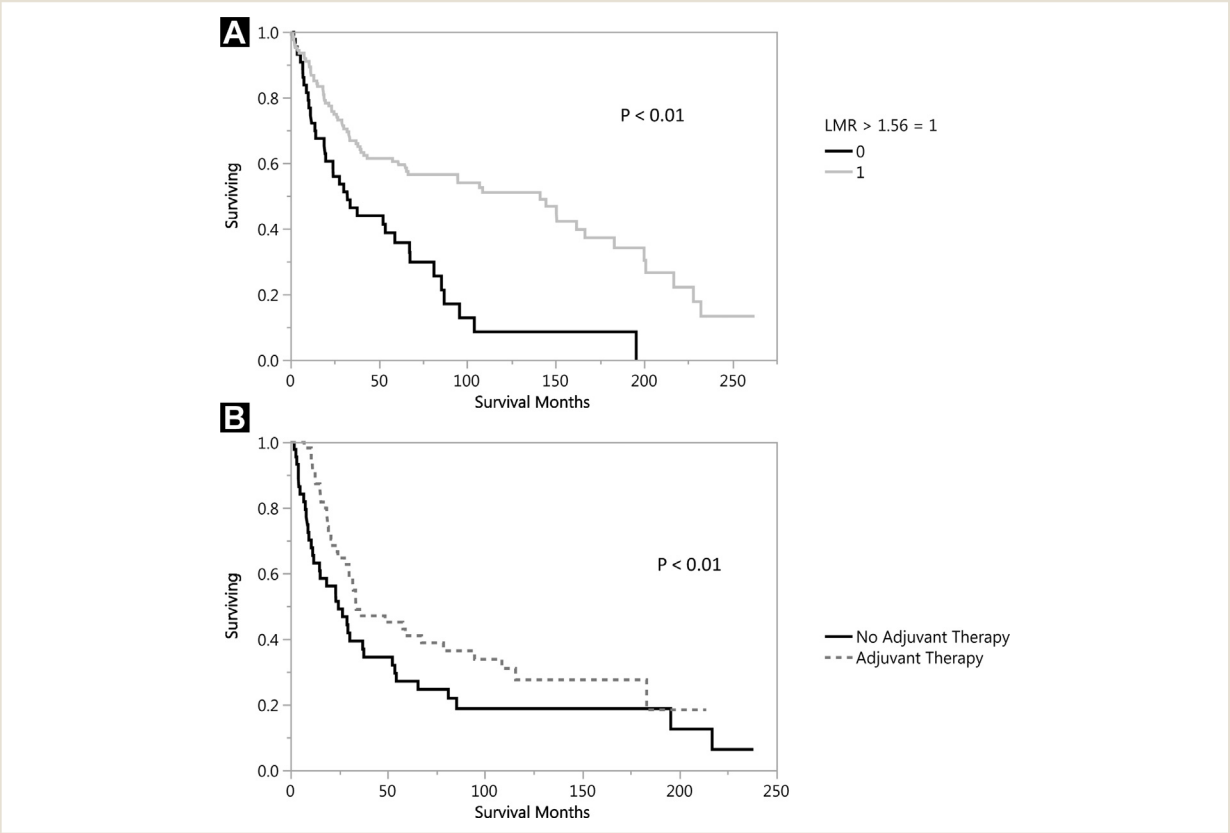
We identified 241 patients with stage I-III SBA who underwent resection at Mayo Clinic in Rochester, MN. The tumors most commonly originated in the duodenum, followed by jejunum and ileum (64.7%, 23.2%, and 9.1%, respectively) (Table 1). Median

Table 2 Survival According to Cancer Stage and Adjuvant Therapy

	Adjuvant Therapy		No Adjuvant Therapy		
AJCC Stage	MS (Months)	5OS (%)	MS (Months)	5OS (%)	*P*
I	UR	100	201	86	.39
II	144.6	56	53.2	47	.14
III	33.8	39	24.7	25	<.01[a]
All	59.1	48	54.5	50	.17

Abbreviations: AJCC = American Joint Commission on Cancer; 5-OS = 5-year overall survival; MS = median overall survival; UR = unreached.
[a]Statistically significant ($P < .05$).

Figure 2 Kaplan-Meier Survival Curves Demonstrating OS by (A) LMR in All Patients and (B) Adjuvant Therapy in Patients With Stage III Disease. (A) Presurgical LMR > 1.56 to < 1.56; Median OS for LMR > 1.56 Was 141 Months (95% CI, 61.2-167) Versus LMR < 1.56, 32.2 Months (95% CI, 19.1-67.4) ($P < .01$). (B) Adjuvant Therapy Median OS With Adjuvant Therapy Was 33.8 Months (95% CI, 27.8-78.8) Versus No Adjuvant Therapy, 24.7 Months (95% CI, 11.5-37.8) ($P < .01$)



Abbreviations: CI = confidence interval; LMR = lymphocyte-to-monocyte ratio; OS = overall survival.

age at diagnosis was 65 years (range, 25-92 years). Most commonly, tumors had grade 3 differentiation (59.1%), followed by grades 2 (28.2%) and 4 (10.8%). Grade 1 differentiation was uncommon. T3 stage (invading through the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue with extension 2 cm or less) was most common (47.6%), followed by T4, T2, and T1.[20]

Overall Survival

Median OS for the entire group was 54.5 months (95% confidence interval [CI], 37.2-81.2 months), with 5- and 10-year OS of 48% and 35%. Median follow-up was 113.7 months (95% CI, 97.9-126.6 months). Median OS for all stage I disease was 201 months (95% CI, 107-232 months), stage II disease 61 months (95% CI, 33-117 months), and stage III disease 32 months (95% CI, 24.5-49 months) (Figure 1).

Adjuvant Therapy

Factors associated with increased likelihood of receiving adjuvant therapy included younger age (57 vs. 68 years), higher grade tumors, higher T stage, and higher N stage (Table 1). Median OS in patients with stage III disease was 33.8 months in those who received adjuvant therapy compared to 24.7 months in those who did not receive adjuvant therapy ($P < .01$) (Table 2). There was no demonstrated benefit in patients with stage I or stage II disease. FOLFOX was provided to 22 patients and 5-FU in 25 patients. Other less commonly used treatments included capecitabine/oxaliplatin, capecitabine alone, oxaliplatin alone, and irinotecan alone. When compared to no therapy at all, FOLFOX was associated with improved OS in patients with stage III disease (hazard ratio [HR] = 0.39; 95% CI, 0.14-0.87; $P = .02$).

Univariate and Multivariate Predictors of Survival

Male sex, advanced T stage, advanced N stage, positive lymph node ratio, LMR < 1.56, presence of residual disease, and earlier date of diagnosis predicted worse survival on univariate analysis. The overall area under the curve for LMR was 0.63 ($P < .01$) (specificity 37.3%, sensitivity 90.1%, positive predictive value 33.1%, and negative predictive value 92.2%). There were 126 patients with LMR > 1.56 and 43 patients with LMR < 1.56 in the entire cohort. LMR < 1.56 was an independently poor prognostic factor (HR = 2.20; 95% CI, 1.27-3.84; $P < .01$)

Table 3 Univariate and Multivariate Analysis

	All Patients				No Adjuvant Therapy				Adjuvant Therapy			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
Characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex												
Female	1.0 (reference)	.04[a]		.17		.07		.15		.49		.96
Male	1.43 (1.01-2.02)											
Age												
<60 y			1.0 (reference)		1.0 (reference)		1.0 (reference)					
>60 y		.05	1.79 (1.09-2.93)	.02[a]	2.45 (1.38-4.35)	<.01[a]	5.09 (1.89-13.7)	<.01[a]		.51		.80
T Stage												
T1	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)					
T2	1.54 (0.46-5.1)	<.01[a]	1.40 (0.4-4.9)	.04[a]	1.02 (0.27-3.8)	<.01[a]	1.04 (0.25-4.36)	<.01[a]		.23		.82
T3	3.58 (1.31-9.8)		2.4 (0.8-7.2)		3.54 (1.27-9.9)		2.96 (0.91-9.6)					
T4	4.84 (1.75-13.3)		3.38 (1.13-10.2)		5.16 (1.83-14.6)		6.04 (1.78-20.5)					
N Stage												
N0	1.0 (reference)				1.0 (reference)				1.0 (reference)		1.0 (reference)	
N1	1.47 (1.0-2.16)	<.01[a]		.14	1.8 (1.09-3.0)	.02[a]		.58	1.44 (0.71-2.92)	.03[a]	0.83 (0.22-3.1)	<.01[a]
N2	2.28 (1.45-3.59)				2.24 (1.15-4.4)				2.63 (1.27-5.45)		7.3 (1.1-47.8)	
Lymph Node Ratio												
>10%	1.0 (reference)	<.01[a]		.50	1.0 (reference)	.01		.31	1.0 (reference)	.01		.52
<10%	1.91 (1.35-2.72)				1.93 (1.18-3.15)				2.13 (1.17-3.9)			
Location												
Duodenum												
Jejunum		.20		.68		.48		.31		.35		.31
Ileum												
LMR												
LMR > 1.56	1.0 (reference)	<.01[a]	1.0 (reference)	<.01[a]	1.0 (reference)	<.01[a]			1.0 (reference)	<.01[a]	1.0 (reference)	<.01[a]
LMR < 1.56	2.40 (1.57-3.67)		2.20 (1.27-3.84)		2.06 (1.22-3.48)			.17	4.71 (2.08-10.66)		6.8 (2.54-18.2)	
Margin Status												
R0	1.0 (reference)	<.01[a]		.76	1.0 (reference)	<.01		.41	1.0 (reference)	<.01		NA
R1	3.2 (1.9-5.45)				2.8 (1.55-4.96)				25.7 (4.9-134.6)			
Date of Diagnosis												
Before 2006	1.0 (reference)	.02[a]		.81		.11		.95		.09		.45
After 2006	0.66 (0.46-0.96)											

Table 3 Continued

Characteristic	All Patients				No Adjuvant Therapy				Adjuvant Therapy			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Adjuvant Therapy												
Yes												
No		.41		.18								

Abbreviations: CI = confidence interval; HR = hazard ratio; LMR = lymphocyte-to-monocyte ratio.
*Statistically significant ($P < .05$). *P* values were generated by likelihood ratio tests.

(Figure 2A). Tumor grade, age, location, date of diagnosis, type of surgery, and adjuvant chemotherapy use were not associated with OS among all patients. Peripheral blood cell markers including neutrophil and eosinophil counts were not statistically significant for the training cohort, so they were not included in the validation analysis. After adjustment for other demographic factors, age > 60 years (HR = 1.79; 95% CI, 1.09-2.93; $P = .02$), LMR < 1.56 (HR = 2.20; 95% CI, 1.27-3.84; $P < .01$), and advanced T stage (HR = 3.38; 95% CI, 1.13-10.2) were identified as independent negative predictors of OS (Table 3). In patients who received adjuvant therapy, advanced N stage (HR = 7.3; 95% CI, 1.1-47.8) and LMR < 1.56 (HR = 6.8; 95% CI, 2.54-18.2; $P < .01$) were independent negative predictors of OS.

Discussion

In this large series of patients, we found 241 patients with resected SBA (stages I-III) during a 22-year period. We identified LMR as a novel predictor of survival. Our data also suggest an association with improved survival in patients with stage III disease with the use of adjuvant chemotherapy.

In a previously published cohort of patients from Mayo Clinic, there was a statistical advantage to chemotherapy in metastatic disease only, not in patients with earlier stage disease.[19] In this updated population of a portion of those patients in addition to patients diagnosed the following decade (2006-2015), we confirmed an improvement in survival for patients with stage III disease who received adjuvant therapy after surgical resection (median OS, 33.8 vs. 24.7 months; $P = .01$) (Figure 2B). More specifically, our data suggest that FOLFOX therapy in patients with stage III disease was associated with improved OS compared to no therapy. These findings support practice changes surrounding clinical studies that suggested combination 5-fluoropyrimidine and platinum therapy improved OS in patients with metastatic SBA along with data suggesting OS benefit in patients with colorectal adenocarcinoma.[22-24] Adjuvant chemotherapy has been used mostly for high-risk, typically node-positive disease in SBA.[7,25] Use of adjuvant therapy is mostly supported in the medical literature by small retrospective analyses for SBA specifically. There is a prospective analysis of resectable SBA that primarily included patients with periampullary tumors without any inclusion of primary jejunum or ileum adenocarcinoma, which suggested a benefit of adjuvant therapy.[6] BALLAD trial is an ongoing phase 3 trial that is evaluating the role of adjuvant chemotherapy in patients with resected small bowel cancer (ClinicalTrials.gov NCT02502370).

In our study, the benefit of adjuvant therapy was restricted to patients with stage III disease, which supports large database analyses.[5] There seems to be an improvement in OS over recent years as well. In fact, there was a statistically significant improvement in OS when comparing SBA diagnosed before 2006 to SBA diagnosed after 2006 ($P = .02$). There are many possibilities for this finding that include earlier recognition or diagnosis of the small intestine tumors and more careful selection of patients receiving adjuvant therapy. For instance, 20.6% versus 10.4% were stage I and 39% versus 32% were stage II (disease diagnosed after 2006 vs. before 2006). In addition, patients who received adjuvant therapy primarily received FOLFOX after 2006 (n = 22) compared primarily with chemoradiation (n = 25) or single-agent 5-FU (n = 25) before 2006.

Additionally, in our cohort, there was a survival benefit for patients with T4 tumors who received adjuvant therapy as well ($P = .04$). Recent French guidelines suggest adjuvant therapy in patients with T4 tumors, which our data support.[12] After controlling for demographic factors, we found that advanced age, advanced T stage by American Joint Committee on Cancer (AJCC) criteria, and lower LMR were independent negative predictors of OS (Table 3). These findings are consistent with prior studies.[3,13-15,19] Herein, we have also described a new prognostic factor for predicting survival in early stage SBA: LMR. LMR as a prognostic factor was initially described in classical Hodgkin lymphoma, and it has since been described in at least 14 solid tumors, including colorectal adenocarcinoma.[16,17,26,27] On a pathophysiologic level, the tumor microenvironment includes tumor-infiltrating lymphocytes and macrophages, though the medical literature is unclear of their prognostic value.[28] Tumor-associated macrophages, which are differentiated monocytes, have been implicated in worsening tumor progression. Poor outcomes have also been associated with increased tumor associated macrophages in colorectal adenocarcinoma.[27] Meanwhile, increased intratumoral lymphocytes have been associated with improved OS.[29] The association of LMR with OS presents an interesting hypothesis, possibly suggesting a peripheral marker of how tumors are interacting with the immune system. LMR seems to indicate response to certain therapy in some malignancies, and chemotherapy's effect on the immune system may modulate tumor killing.[30] LMR could potentially be used to determine possible response to immunotherapy.[16] At this point, though, it is unclear how to best take advantage of the LMR, and additional validation studies are needed.

There are several limitations to our study. This is a retrospective cohort of patients and thus subject to several possible biases, which include lead-time bias and selection bias. Also, the AJCC staging criteria have changed over time. However, we updated the staging for every patient using the most recent AJCC staging system. Even though this is one of the largest single-institution series reported, more robust results may be obtained with more patients. In terms of adjuvant therapy, there were missing data for a small portion of patients who received adjuvant therapy outside our institution.

Conclusion

Early stage SBA is a rare malignancy that requires further prospective study. We updated survival patterns over the past 20 years at Mayo Clinic, demonstrating a survival advantage for patients with stage III disease receiving adjuvant therapy. On the basis of our experience, FOLFOX should be considered for adjuvant therapy in stage III disease. In addition, LMR is a novel prognostic factor in these patients. Our findings should be validated in a prospective randomized trial.

Clinical Practice Points

- SBA is a rare malignancy affecting approximately 3000 patients per year. Current standard of therapy includes resection and adjuvant chemotherapy in high-risk disease, though the benefits are unclear.
- LMR, age, and T stage independently predict survival in patients with resected SBA.
- Adjuvant chemotherapy with a fluoropyrimidine-and-platinum regimen could be considered in resected stage III SBA.

Disclosure

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

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