

Clinical features and prognostic factors in small bowel tumors: A retrospective evaluation of eighty cases

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Abstract

Aim: Small bowel tumors are rare tumors originating from the gastrointestinal tract. In this study, we aimed to determine the clinical characteristics and prognostic factors effecting survival in patients with small bowel cancer.

Material and Methods: Eighty patients with small bowel malignancy between February 2002 and December 2016 were evaluated retrospectively. Clinical characteristics, pathological features, laboratory results, progression-free and overall survival rates were determined. The effect of the evaluated parameters on survival was examined.

Results: The incidence of small bowel tumors was 0.36% in patients admitted to our clinic. The median age of the patients was 55 and 68.8% of the patients were male. The most common histologic subtype was adenocancer (42.5%), and the most common localization site (37.5%) was duodenum. 27 of patients (33.8%) had metastasis at the time of diagnosis. The most common site of metastasis was liver. Overall survival rate was 59.1% in the third year and 52.9% in the fifth year. The median disease-free survival (DFS) rate was 78% in the third year and 68% in the fifth year.

Conclusion: Information about these tumors is limited in the literature and was presented in retrospective case series. In our study, the most common localization site was found as duodenum and the most common histological type was adenocancer. Prognosis of patients undergoing curative surgical resection was found to be better.

Key words: Small bowel tumors; prognostic factors; adenocancer

INTRODUCTION

Tumors of the small bowel are very rare. Although 75% of the digestive system length and 90% of the surface area are small bowels, only 0.5-1% of all digestive system tumors originate from the small bowel. It is most commonly seen in the 5th and 6th decades and 1.5 times more frequent in men than in women (1).

93% of small bowel tumors are carcinoid tumor, adenocarcinoma, lymphoma and gastrointestinal stromal tumors (GIST), which are 4 major subtypes. The remaining 7% have more than 40 histological subtypes (2).

Advanced age, hereditary syndromes, inflammatory bowel diseases, celiac disease, immunosuppression, alcohol use and obesity are risk factors for small bowel malignancies (3).

Rare occurrence of small bowel cancers and nonspecific symptoms cause late diagnosis. The most common presenting symptoms are abdominal pain; the most common clinical finding is pale appearance (4).

The American Joint Commission on Cancer (AJCC) staging system is used for staging small bowel adenocarcinoma (5). There is a negative correlation between stage and survival (6).

Considering the fourfold increase in carcinoid cases over the past 20 years, carcinoids are the most common small bowel cancer in the United States (US) according to the National Cancer Database. (7,8).

Marginal zone B cell lymphomas are a type of mucosal lymphoid tissue (MALT) type Non-Hodgkin's Lymphomas (NHL) and are the most common primary gastrointestinal lymphomas. The most important prognostic indicator

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of small bowel lymphoma is tumor dissemination. Most gastrointestinal lymphomas are NHL and the Ann Arbor staging system is used for staging (9).

GISTs are the most common mesenchymal tumors of the small bowel, although they constitute only 0.5-1% of all gastrointestinal tumors. 30% to 50% of GISTs are clinically malignant (10). Tumor location, tumor size and mitotic activity play an important role in determining prognosis (11).

We aimed to investigate the etiologic, demographic and clinical characteristics of patients with small bowel cancer who applied to our clinic and to determine prognostic factors effecting survival.

MATERIAL and METHODS

Eighty patients with small bowel malignancy between February 2002 and December 2016 in Ankara Numune Education and Research Hospital Oncology Clinic were included in the study. Periapillary region and ampulla vateri tumors were excluded. Demographic, clinical, pathology and follow-up data of the patients were evaluated retrospectively.

Eastern Cooperative Oncology Group (ECOG) performance scale was used to determine the performance status of the patients (12). The staging of patients with small bowel adenocarcinoma, gastrointestinal stromal tumor and neuroendocrine tumor was performed using the 7th AJCC Staging System. The staging of patients with non-Hodgkin lymphoma was performed using the Ann – Arbor Staging System. Information about the patients' life situations was obtained from hospital automation system records and death notification system.

Eight patients were not included in the survival analysis because they did not have identification numbers or were seen only once in our clinic. Survival analysis was performed on 72 patients.

Overall survival was calculated as the time from the date of diagnosis to death or to the last control, at the end of the study, the period of time until the patient information was updated was taken as the basis for the patients who were still alive. Disease-free survival was calculated for patients who underwent curative resection but without metastasis, and progression-free survival was calculated for patients who didn't undergo curative resection or had metastasis. Progression-free survival was calculated in months based on the time from date of diagnosis to progression or death. Disease-free survival was calculated in months based on the time from diagnosis date to death or last control date.

The duration of relapse-free survival was calculated in months for patients with a diagnosis of non-Hodgkin lymphoma based on the time from complete remission to relapse/death or the last control date.

Ethics Committee approval of Ankara Numune Education and Research Hospital was obtained for the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS for Windows Version 22.0. Numerical variables were summarized with mean \pm standard deviation and (minimum - maximum) values. Categorical variables were represented by numbers and percentages. The overall survival and disease-free survival times were estimated by Kaplan Meier product limit estimation method. Survival curves of different groups were compared with log rank test. Chi Square test was used for comparison between groups and One Way Anova test was used for comparison of numerical and median values. Significance level was taken as $p < 0.05$

RESULTS

Fifty-five patients (68.8%) were male. The median age was 55 (14-83 years). The most common histologic subtype was adenocancer in 34 (42.5%) patients. All of the sarcomas were gastrointestinal stromal tumors. The characteristics of the patients according to tumor subtypes were evaluated with comparison and shown in Table 1.

The median time from onset of symptoms to diagnosis was 1.5 (1-12 months) months. 27 patients (33.8%) had metastasis findings at the time of diagnosis. The most common site of metastasis was liver. Tumor resection was performed in 56 (70%) patients at the time of diagnosis, and palliative surgery was applied to 2 patients (2.5%).

At diagnosis, 48 (60%) patients had hemoglobin values above 10 g/dl, and albumin levels were below 3.5 g/dl in 17 (21.3%) patients. At the time of diagnosis, 3 (3.8%) patients were stage 1, 25 (31.3%) patients were stage 2, 8 (10%) patients were stage 3 and 25 (31.3%) patients were stage 4.

In the whole patient group, 9 (11.3%) patients had lymphatic invasion, 8 (10%) patients had vascular invasion, and 5 (6.3%) had surgical margin positivity.

When the whole patient group was evaluated, only 1 patient received neoadjuvant chemotherapy. 53 (66.3%) patients received adjuvant or palliative chemotherapy. Eleven patients (13.8%) received radiotherapy.

24 (70.6%) of the adenocarcinoma patients received chemotherapy. The majority of patients (32.4%) received 5 FU \pm cisplatin regimen. 7 patients (20.6%) received second line treatment because of relapse or progression.

18 of NHL patients (90%) underwent chemotherapy. One (5%) patient refused treatment and chemotherapy couldn't be started. Treatment data of one patient (5%) could not be reached. Of the 12 patients whose response evaluation data were available, 9 (75%) had complete response. 1 patient (5%) had stable disease and 2 patients (10%) had progression. Because of relapse or progression during the follow-up, 4 patients underwent second-line chemotherapy protocol.

Table 1. The characteristics of the patients according to tumor subtypes

Characteristics	Tumor Subtype				Total n (%)	p*
	Adenocancer n (%)	Sarcoma n (%)	NET n (%)	NHL n (%)		
Patient number	34 (42.5%)	18 (22.5%)	8 (10%)	20 (25%)	80 (100%)	
Gender						
Male	23 (67.6%)	11 (61.1%)	7 (87.5%)	14 (70%)	55 (68.8%)	0.60
Female	11 (32.4%)	7 (38.9%)	1 (12.5%)	6 (30%)	25 (31.3%)	
Median Age (min-max)	59 (30-79 age)	54 (22-72 age)	65.5 (48-83 age)	47 (14-81 age)	55 (14-83 age)	0.04
Smoking						
Yes	15 (44.1%)	4 (22.2%)	3 (37.5%)	6 (30%)	28 (35%)	0.41
No	15 (44.1%)	12 (66.7%)	3 (37.5%)	7 (35%)	37 (46.3%)	
Unknown	4 (11.8%)	2 (11.1%)	2 (25%)	7 (35%)	15 (18.8%)	
Presenting Symptom						
Abdominal pain	19 (55.9%)	8 (44.4%)	4 (50%)	7 (35%)	38 (47.5%)	
Bleeding	-	2 (11.1%)	2 (25%)	1 (5%)	5 (6.3%)	
Weakness	5 (14.7%)	1 (5.6%)	-	2 (10%)	8 (10%)	0.20
Weight loss	2 (5.9%)	1 (5.6%)	-	3 (15%)	6 (7.5%)	
Other	4 (11.8%)	4 (22.2%)	1 (12.5%)	4 (20%)	13 (16.4%)	
Unknown	4 (11.8%)	2 (11.1%)	1 (12.5%)	3 (15%)	10 (12.5%)	
Diagnostic Method						
Primary tumor resection	15 (44.1%)	16 (88.9%)	7 (87.5%)	13 (65%)	51 (63.8%)	0.03
Biopsy	16 (47.1%)	1 (5.6%)	1 (12.5%)	3 (15%)	21 (26.3%)	
Unknown	3 (8.8%)	1 (5.6%)	-	4 (20%)	8 (10%)	
Tumor Localization						
Duodenum	23 (67.6)	2 (11.1%)	2 (25%)	3 (15%)	30 (37.5%)	
Jejunum	6 (17.6%)	10 (55.6%)	2 (25%)	5 (25%)	23 (28.7%)	0.001
Ileum	1 (2.9%)	2 (11.1%)	2 (25%)	3 (15%)	8 (10%)	
Unknown	4 (11.8%)	4 (22.2%)	2 (25%)	9 (45%)	19 (23.8%)	
Acute Abdomen	5 (14.7%)	0	1 (12.5%)	3 (15%)	9 (11.3%)	0.34
ECOG						
0-1	20 (58.8%)	16 (88.9%)	8 (100%)	13 (65%)	57 (71.3%)	0.02
2-3	10 (29.3%)	-	-	5 (25%)	15 (18.8%)	
Unknown	4 (11.8%)	2 (11.1%)	-	2 (10%)	8 (10%)	

* Chi-square test was applied

17 of 18 patients with GIST underwent surgery and 9 of these 17 patients received adjuvant imatinib treatment. Sunitinib treatment was given to 2 of the patients who received imatinib treatment because of relapse or progression.

Curative resection was performed in 5 of 8 patients with carcinoid tumors and 2 of these patients received systemic chemotherapy. One patient received cisplatin + etoposide and the other received 5-FU + adriamycin.

Table 2. Parameters that significantly effected overall survival with univariate analysis

Parameter	Median survival (95% CI)	p *
ECOG		
0-1	96.2 (56.2-136.2)	0.011
2-3	14.4 (2.6-26.2)	
Diagnosis Stage		
1-2	96.2 (-/-)	0.009
3-4	19.2 (9.6-28.8)	
Diagnostic Method		
Operation	106.5 (32.5-180.517)	0.001
Biopsy	12.4 (4.5-20.3)	
Localization		
Duodenum	17.3 (7.4-27.3)	<0.0001
Jejunum	106.5 (87.3-125.6)	
Ileum	NA	
Pathology		
Adenocancer	17.3 (8.6-26.0)	<0.0001
NET	106.5 (45.6-167.3)	
Sarcoma	NA	
NHL	139.4 (9.2-269.6)	
Curative Resection		
Yes	14.4 (3.0-25.8)	0.001
No	96.2 (25.1-167.3)	
Metastasis		
Yes	NA	0.009
No	19.9 (5.2-34.5)	
Smoking		
Yes	96.2 (8.2-184.2)	0.032
No	22.6 (10.8-34.4)	
Albumin		
<3.5 g/dl	6.4 (0-17.4)	0.005
>3.5 g/dl	75.3 (43.9-106.8)	

* Log-Rank test was applied.

Table 3. Parameters that didn't significantly affect overall survival with univariate analysis

Parameter	Median survival (95% CI)	p *
Gender		
Male	67.4 (25.4-109.5)	0.767
Female	96.2 (8.0-184.4)	
Hemoglobin		
>10 g/dl	75.3 (34.4-116.2)	0.464
<10 g/dl	96.2 (7.3-185.1)	
Surgical margin		
Pozitive	NA	0.826
Negative	96.2 (43.0-149.4)	

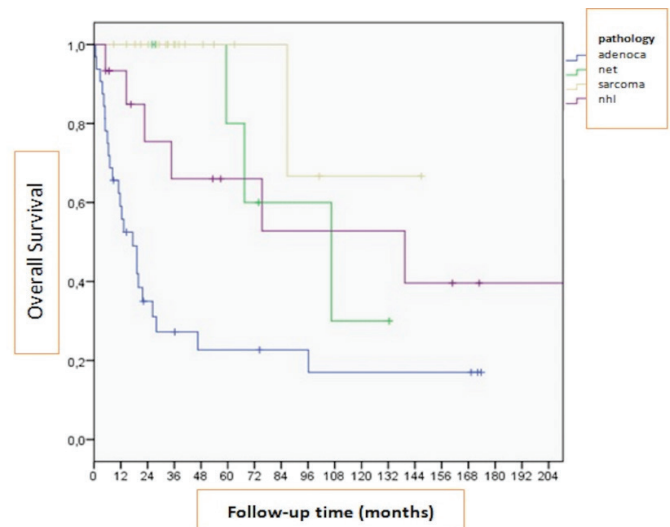
* Log-Rank test was applied

Survival Analysis

The median follow-up was 23.5 months (1-331 months). During the follow-up period, 34 patients died and 38 survived. Therefore, median overall survival could not be achieved. Overall survival rate was 59.1% in the third year and 52.9% in the fifth year. The median progression-free survival (PFS) for metastatic patients (n = 30) was 19.2 months (95% CI 4.5-33.9). The median disease-free survival (DFS) for patients undergoing curative surgery (n = 27) could not be achieved. Recurrence occurred in 6 patients during the follow-up period. DFS rate was 78% in the third year and 68% in the fifth year.

The 5-year relapse-free survival rate was 87.5% in patients with non-Hodgkin's Lymphoma (n = 15).

As a result of the analysis; stage, ECOG performance status, tumor type, surgical resection, albumin value at the time of diagnosis, presence of metastasis and smoking was found to have statistically significant effect on overall survival (p<0.05). Overall survival curve according to tumor type was shown in Figure 1. Gender, hemoglobin level at the time of diagnosis and surgical margin positivity didn't have statistically significant effect on overall survival (p>0.05). Parameters that effected overall survival were shown in Table 2 and Table 3, respectively.

**Figure 1.** Overall survival curve according to tumor type

DISCUSSION

Tumors of the small bowel are very rare. Patients present with nonspecific symptoms and therefore the diagnosis is delayed. The time from admission to diagnosis was reported to be approximately 30 weeks (13). On the other hand, it was reported that the delay in diagnosis due to the inability of patients to express their symptoms was less than 2 months in another study (14). In our study, the median time from onset of symptoms to diagnosis was 1.5 months (1-12 months). In the study of Minardi et al., the time from the onset of symptoms to surgery was

reported as 54 days (15).

In our study, 55 patients were male and the number of male patients was 2.2 times higher. In a study conducted by Bilimoria et al. between 1985 and 2005 with 67,843 patients, small bowel cancer was found to be more frequent in men than in women (16).

Tobacco use was associated with increased risk of small bowel cancer in 2 studies, while other studies showed no increased risk in smokers (17-19). In our study, 28 (35%) of the patients included in the study had active smoking and smoking had a negative effect on overall survival.

Although the incidence of adenocarcinoma has historically been higher than carcinoid tumors, this has changed in favor of carcinoid tumors in the last decade. In 1987, according to the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute, the most common histological type in small bowel tumors was adenocarcinoma with 45% rate. This was followed by carcinoid 29%, lymphoma 16% and sarcoma 10%, respectively (20). In 2000, carcinoid tumors were reported to be higher than adenocarcinoma. In our study, 34 (42.5%) patients had adenocarcinoma, 20 (25%) NHL, 18 (22.5%) sarcoma and 8 (10%) neuroendocrine tumor diagnosis. Although the ratio has shifted to the carcinoid direction in recent years, adenocarcinoma superiority was still present in our patients. It was thought that this difference between literature and our study was because our study did not show the current distribution due to the small number of patients, or that the differences in geographical and dietary factors, smoking and alcohol use status may have affected the epidemiological data. At the same time, it was thought that many patients with carcinoid tumors was operated in surgical clinics and wasn't referred to the oncology clinic.

When the tumor site is examined, approximately 50% of small bowel tumors are located in the duodenum where adenocarcinomas are dominant (16). According to our tumor localization data, the tumor was localized in the duodenum in 30 (37.5%) patients. When tumor subtypes were evaluated in terms of localization, it was seen that adenocarcinoma were mostly located in duodenum and jejunum was the most common site for sarcoma and NHL. The results are similar to the results in our study.

In our study, although the age of diagnosis and gender didn't have a significant effect on overall survival, it was seen that male gender reduced survival. However, in a study conducted by Bilimoria et al. in 1440 centers in 2009, it was reported that advanced age and male sex caused a poor prognosis in all tumor subtypes (16). In another study, it was reported that age didn't have a significant effect on survival (21).

In our study, the histological subtype of the tumor had a statistically significant effect on overall survival. The median survival of adenocarcinomas was the shortest survival time with 17.3 months. The literature also shows that adenocarcinoma have a negative effect on survival compared to other histological subtypes (16).

When the laboratory parameters were examined, it was seen that the survival of 17 (21.3%) patients with albumin values less than 3.5 g/dl decreased statistically significantly. Although hemoglobin value didn't have a statistically significant effect on survival, it was found that the survival of 61.1% patients with hemoglobin values higher than 10 g/dl was found to be decreased. When literature data were examined, it was seen that survival analysis wasn't performed with laboratory parameters in small bowel tumors.

In our study, there was no statistically significant difference between the groups in terms of pathological parameters. However, there are studies in the literature showing that surgical margin positivity decreases prognosis (16). A small number of patients undergoing surgical resection may have caused the difference.

The presence of metastasis in adenocarcinoma patients had a significant effect on survival. In the study conducted by Aydin et al., the presence of metastasis was found to negatively affect survival as in our study (22).

CONCLUSION

As a result of our study, the patients with small bowel cancer treated in our center were examined in terms of etiological, demographic and clinical features and we determined the prognostic factors effecting survival. Stage, ECOG performance status, tumor type, surgical resection, albumin value at the time of diagnosis, presence of metastasis and smoking were significant effect on overall survival. When we compare the current literature data with the results of our study, we observed that prospective studies with more patients are needed to determine the prognostic factors effecting survival more clearly.

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