ORIGINAL RESEARCH

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Clinicopathological Features and Prognostic Factors in Patients with Small Bowel Adenocarcinoma

İnce Bağırsak Adenokarsinomlu Hastalarda Klinikopatolojik Özellikler ve Prognostik Faktörler

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Abstract

Objective: Small bowel adenocarcinoma is a rare tumor, and data on prognosis are limited. We aimed to evaluate the clinicopathological features and prognostic factors in small bowel adenocarcinoma in this study.

Method: Twenty-two patients were evaluated. Clinicopathological features and treatment approaches were retrospectively recorded. The Kaplan-Meier and Cox regression analyses were used to assess overall survival and prognostic factors.

Results: The origin sites of the tumor were the duodenum (50%), jejunum (31.8%), and ileum (18.2%), respectively. The number of *de novo* metastatic patients was 11 (50%). The most common metastatic sites were the peritoneum (%45), liver (%41), and lymph nodes (18%). The median overall survival was 19.9 months (7.3-32.5). One- and two-year survival ratios were 65.9% and 39%, respectively. The response ratio (complete or partial) of first-line chemotherapy in metastatic patients was determined as 46.2%. In multivariate analysis, surgery (p=0.024) and age at diagnosis (p=0.017) were statistically significant prognostic factors for overall survival. However, the site of the tumor (p=0.106), *de novo* metastatic disease (p=0.323), and the number of metastatic sites (p=0.086) were not.

Conclusion: Patients with small bowel adenocarcinoma were diagnosed in advanced stages, and the prognosis of the disease was poor. We observed that removing the primary tumor improved survival, and being older than 60 years was a negative prognostic factor.

Keywords: Chemotherapy, prognosis, small bowel adenocarcinoma

Öz

Amaç: İnce bağırsak adenokarsinomu nadir görülen bir tümördür ve prognozu ile ilgili veriler sınırlıdır. Bu çalışmada ince bağırsak adenokarsinomlu hastalarda klinikopatolojik özellikleri ve prognostik faktörleri değerlendirmeyi amaçladık.

Yöntem: Yirmi iki hasta değerlendirildi. Klinikopatolojik özellikler ve tedavi yaklaşımları retrospektif olarak kaydedildi. Genel sağkalımı ve prognostik faktörleri değerlendirmek için Kaplan-Meier ve Cox regresyon analizleri kullanıldı.

Bulgular: Tümörün primer çıkış yerleri sırası ile duodenum (%50), jejunum (%31,8) ve ileum (%18,2) idi. *De novo* metastatik hasta sayısı 11 (%50) idi. En sık metastatik bölgeler sırası ile periton (%45), karaciğer (%41) ve lenf düğümleri (%18) idi. Medyan genel sağkalım süresi 19,9 aydı (7,3-32,5) idi. Bir ve iki yıllık sağkalım oranları sırasıyla %65,9 ve %39 olarak bulundu. Metastatik hastalarda birinci basamak kemoterapinin yanıt oranı (tam veya kısmi yanıt) %46,2 olarak tespit edildi. Çok değişkenli analizde cerrahi (p=0,024) ve tanı yaşı (p=0,017) genel sağkalım için istatistiksel olarak anlamlı prognostik faktörler olarak tespit edildi. Ancak primer tümör bölgesi (p=0,106), *de novo* metastatik hastalık (p=0,323) ve metastatik bölge sayısı (p=0,086) istatistiksel olarak anlamlı değildi.

Sonuç: İnce bağırsak adenokarsinomlu hastalara sıklıkla ilerlemiş hastalık ile tanı konulmuştu ve hastalığın prognozu kötüydü. Primer tümörün çıkarılmasının sağkalımı iyileştirdiğini ve tanı sırasında 60 yaşından büyük olmanın olumsuz bir prognostik faktör olduğunu tespit ettik.

Anahtar kelimeler: İnce bağırsak adenokarsinomu, kemoterapi, prognoz

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Introduction

Small bowel tumors are rare and account for less than 1% of all cancers and approximately 2% of gastrointestinal tract tumors (1,2). Several theories have been proposed to explain the rarity of small bowel tumors. The small intestines have more fluid content and are exposed to less irritants, the bacterial load is less, and the protective effect of the lymphatic tissue may be one of the reasons for this less frequent tumor development (3-5). It can be seen with a large number of different types of tumors, including benign and malignant, in the small intestines. Malignant tumors of the small intestine are frequently adenocarcinoma, neuroendocrine tumors, and lymphomas. While adenocarcinoma is observed more frequently in the duodenum and jejunum, neuroendocrine tumors are more commonly diagnosed in the ileum (6). Due to its rarity, it was obtained from risk factors and registry analyses in patients with small bowel cancer. It has been stated that alcohol consumption, smoking, dietary characteristics, and Celiac disease pose a risk for the development of small bowel cancer (7-9). Small bowel cancers can present with very variable non-specific symptoms at diagnosis. Therefore, there is often a delay in its diagnosis. Abdominal pain, nausea, vomiting, weight loss, dyspepsia, and anemia-related symptoms may be associated with small bowel cancer. Moreover, patients may appear with intestinal obstruction and bowel perforation due to the difficulties and delay in diagnosis.

Surgery is the primary treatment for small bowel adenocarcinoma (SBA). Adjuvant or neoadjuvant treatments have not been clearly defined. For this reason, it is usually treated similarly to colon cancer. In this perspective, if there is lymph node positivity or T3 and T4 in tumors that have been surgically removed, adjuvant therapy is often given in routine practice. In metastatic disease, fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and irinotecan can be used in different combinations. There are insufficient data on the efficacy and safety of anti-EGFR (cetuximab or panitumumab) and anti-VEGF (bevacizumab and others) agents. Data on the efficacy and safety of immunotherapies have only just begun to be determined. Pembrolizumab was found to be ineffective in a phase 2 study that included previously treated patients with progressive SBA (10). Patients with SBA have a worse prognosis compared to patients with colon cancer. In this study, we aimed to examine the clinicopathological features and prognosis of patients with SBA followed in our clinic.

Materials and Methods

Patients and Data Collection

The data of patients diagnosed and treated in the single tertiary medical oncology outpatient clinic between 2015 and 2019 were reviewed retrospectively. Approval was obtained from the Local Ethics Committee at the İstanbul University, İstanbul Faculty of Medicine before the study (number: 232479). Patients were identified through the hospital information system. All patients with sufficient data were included in the study. Symptoms at the time of diagnosis, clinical (age, gender, stage, metastasis regions, etc.), pathological (tumor region, tumor type, grade, etc.), and treatment characteristics (type of surgery, adjuvant chemotherapy and radiotherapy, metastatic treatment regimens, responses, and adverse events) were recorded from patient files and hospital database. Tumor staging was performed according to the eighth TNM tumor staging system. According to the Eastern Cooperative Oncology Group system, the patient's performance status was determined.

Metastatic patients received different chemotherapy regimens for treatment in the first series. In the FOLFOX regimen, 5-fluorouracil 2.400 mg/m^2, oxaliplatin 85 mg/m^2 and calcium folinate 400 mg/m^2 were administered every two weeks. In the FOLFIRI regimen, 5-fluorouracil 2,400 mg/m^2, irinotecan 180 mg/m^2 and calcium folinate 400 mg/m^2 were administered every two weeks. In the XELOX, XELIRI regimen, capecitabine was administered at a dose of 1,000 mg/m^2 in the morning and evening for 14 days for a 21-day cycle, instead of the 5-fluorouracil. In addition, capecitabine was administered alone at a dose of 1,000 mg/m^2 for a period of 14 days and a 21-day cycle interval. Gemcitabine was given at a dose of 1,000 mg/m^2 on the 1st and 8th days of the 21-day cycle. In the FOLFOX + bevacizumab regimen, bevacizumab was administered at 5 mg/kg dose every 14 days. Treatment response evaluations were performed according to the response evaluation criteria in solid tumors (RECIST). The Common Terminology Criteria for Adverse Events Version 5.0 was used for treatment-related toxicity assessment. Univariate analysis was performed to evaluate the survival effect for all clinicopathological characteristics of the patients. Multivariate analysis was performed for prognostic variables that were found to be

statistically significant in univariate analysis or statistically significant in the literature.

Statistical Analysis

SPSS 25 (IBM, USA) was used for statistical analysis. Descriptive analysis was performed for all variables. For continuous variables, minimum and maximum values were specified, along with the median value. Categorical variables were indicated by numbers and percentages. A log-rank test was performed for survival analysis, and the Kaplan-Meier curve was drawn. The Cox-regression model was applied for univariate and multivariate analysis.

Results

Clinicopathological Features and Treatment Data

Twenty-two patients with small bowel cancer were included in the study. All patients were in the adenocarcinoma histological subtype. The median age was 57 years (27-80). The ratio of males/females was 1.45. The most common symptom in the presentation was pain (50%), and 18% of the patients had ileus. The origin sites of the tumor were the duodenum (50%), jejunum (31.8%), and ileum (18.2%). The number of *de novo* metastatic patients was 11 (50%). Sixteen (72.7%) of the patients underwent surgery. The most common metastatic site was the peritoneum (45%). Clinicopathological characteristics of the patients are presented in Table 1.

Metastatic disease developed in five patients during follow-up, and a total of 16 (72.7%) patients were evaluated for metastatic treatment.

The most commonly used chemotherapy combinations were FOLFOX or XELOX (37.6%), and the second most commonly used regimens were FOLFIRI or XELIRI (12.6%). The disease control rate (complete response, partial response, and stable disease) was determined as 53.8%. Table 2 presents the treatment approach of the patients. The most common hematological side effects included anemia and thrombocytopenia. Non-hematological side effects were nausea and fatigue.

Survival Outcomes and Prognosis

The median follow-up was 14.7 (0.4-72.3) months, and the median overall survival (OS) was defined as 19.9 (7.3-32.5) months. One- and two-year survival ratios were 65.9% and 39%, respectively (Figure 1). In multivariate analysis, surgery (no vs. yes) [p=0.024, hazard ratio: 0.14, 95% confidence interval (CI)] and age at diagnosis (<60 vs. ≥60) (p=0.017, hazard ratio: 11.2, 95% CI) were statistically significant prognostic factors for OS. However, the site of the tumor (p=0.106), *de novo* metastatic disease (p=0.323), and the number of metastatic sites (p=0.086) were not. Table 3 shows the results of univariate and multivariate analyses.

Discussion

In this study, we showed the clinicopathological features of the patients and parameters affecting the prognosis in patients with SBA. Considering data of our study, we found that SBA was seen around the age of 60 years. In our patients, adenocarcinoma of the small intestine was most frequently detected in the duodenum (50%). In a retrospective analysis conducted by Halfdanarson et al. (11), the patient characteristics were similar to our study. The median age of the patients was 62 years, and the tumor localization was in the duodenum, jejunum, and ileum at the rates of 57%, 29%, and 10%, respectively (11). In another study published by Dabaja et al. (12), which included a large number of patients, the median age was 52 years, the most common tumor localization was the duodenum (52%), and 35% of the patients had metastatic disease at diagnosis.

Table 1. Clinicopathological characteristics of the patients

	Number of patients Total number: 22	%
Gender		
Male	13	59
Female	9	41
Tumor localization		
Duodenum	11	50
Jejunum	7	31.8
Ileum	4	18.2
Stage at diagnosis		
Stage 1	1	4.5
Stage 2	3	13.7
Stage 3	7	31.8
Stage 4	11	50
Surgery (primary or palliative) at diagnosis	16	72.7
Yes	6	27.3
No		
Adjuvant chemotherapy after primary surgery		
Yes	11	11
No	11	11
Recurrence after primary surgery		
Yes	6	55
No	5	45
Metastatic sites		
Peritoneum	10	45.5
Liver	9	41
Lymphadenopathy	4	18
Other sites	2	9.1

Table 2. Treatment features of the metastatic patients

	Number of patients (Total number: 16)	%
The first-line chemotherapy regimen		
FOLFOX or XELOX	6	37.6
FOLFIRI or XELIRI	2	12.6
FOLFOX + bevacizumab	1	6.2
FOLFOXURI	1	6.2
Gemsitabin + capecitabine	1	6.2
Gemcitabine	1	6.2
Capecitabine	1	6.2
No therapy	3	18.8
Response ratios of first-line chemotherapy		
Complete response	2	15.3
Partial response	4	30.8
Stable disease	1	7.7
Progression	6	46.2
Grade 1-2 toxicity		
Yes	10	76.9
No	3	23.1
Grade 3-4 toxicity		
Yes	2	15.4
No	11	84.6

Table 3. Univariate and multivariate analyses of prognostic factors for overall survival

	Univariate analysis	Multivariate analysis	
	p	p	Hazard ratio 95% CI
Age (year) <60 vs. ≥60	0.226	0.017	11.2 (1.5-81.8)
Gender Male vs. female	0.784		
Ileus at diagnosis Yes vs. no	0.367		
Primary tumor localization	0.202	0.106	
Tumor grade	0.537		
***De novo* metastatic disease** Yes vs. no	0.328	0.323	
Surgery at diagnosis No vs. yes	0.023	**0.024**	**0.14 (0-0.57)**
Number of metastatic sites	0.982	0.086	

Multivariate analysis p-value: 0.03, CI: Confidence interval

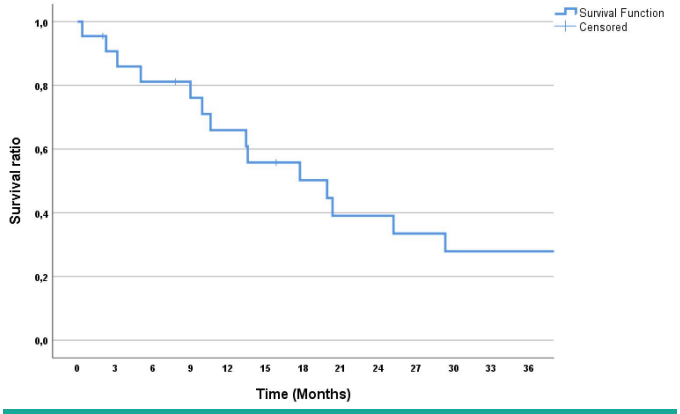

Figure 1. Kaplan-Meier curve for overall survival

Since there is no randomized study for treating patients with SBA, fluoropyrimidine-based therapies are frequently used in the treatment, similar to colon cancer. A phase 2 study published by Xiang et al. (13) showed that the FOLFOX regimen was effective and well-tolerated in patients with advanced SBA. Our patients received more frequently oxaliplatin or irinotecan regimens combined with fluoropyrimidine as chemotherapy. In a multicenter study published by Tsushima et al. (14), in which 132 patients with unresectable SBA were included, the combination of oxaliplatin and fluoropyrimidine was found to be the most promising first-line chemotherapy regimen compared to other chemotherapy regimens. In a multicenter study that included 93 patients published by Zaanan et al. (15), the FOLFOX regimen was found to be more effective than the combination of fluorouracil and cisplatin. In addition, patients' baseline performance scores, CEA, and CA19-9 levels were determined as independent predictive factors for disease-free survival and OS (15). The addition of bevacizumab to the XELOX regimen was found to be effective in a phase 2 study conducted by Gulhati et al. (16), which included 30 patients. However, in a multicenter study of 28 patients published by Aydin et al. (17), adding bevacizumab to the FOLFOX or FOLFIRI regimens did not provide a benefit in terms of disease prognosis.

Patients with SBA have a poor prognosis. Due to delays in diagnosis, most of the patients present in the metastatic stage. Half of the patients had metastatic disease at the time of diagnosis in our study. The median OS was less than two years in the patients. Few studies have examined the prognostic factors in patients with SBA. In our study, patients over the age of 60 years were found to have a higher risk in terms of OS than those younger than 60 years. In addition, patients who did not undergo surgery (primary or palliative) at the time of diagnosis were found to have a poor prognosis. In a study by Aparicio et al. (18), including patients nationwide, the median OS

time of patients with metastatic SBA was found to be 12.7 months, and tumor grade and T-stage were determined as prognostic factors. A retrospective analysis that included a large number of patients by Halfdanarson et al. (11) showed that older age, advanced tumor stage, and a lymph node positivity ratio of 50% or greater were statistically significant factors affecting survival. In a retrospective study including 78 patients, postoperative margin positivity was identified as an independent prognostic factor, and the benefit of adjuvant therapy was not found (19). Contrary to this study, in a study published by Akce et al. (20), it was found that adjuvant chemotherapy improved OS. In another study published by Sakae et al. (21), the presence of symptoms at the time of diagnosis, poor performance status, low albumin level, high CEA level, and LDH level were defined to be poor prognostic factors.

Study Limitations

There were some limitations in our study. Our study was retrospective and included a heterogeneous patient group. The number of patients was small because it is a rare tumor.

Conclusion

Due to the delay in diagnosis, the patients were diagnosed in advanced stages, and the disease was showed a poor prognosis. We observed that removing the primary tumor improved survival, and being older than 60 years was a negative prognostic factor. Also, we detected that tumor localization and *de novo* metastatic disease did not affect OS. To the best of our knowledge, our study is a rare study to describe the characteristics and treatment features of patients with SBA in the Turkish population. It contains essential information about the treatment processes and prognoses of patients with SBA, which seems to be rare. To diagnose and treat SBA more effectively, multicenter randomized controlled studies with large numbers of patients are needed in the future.

Ethics

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee at the İstanbul University, İstanbul Faculty of Medicine before the study (number: 232479).

Informed Consent: For this type of research, informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.D., D.T., Design: İ.D., D.T., Data Collection or Processing: İ.D., D.T., Analysis or Interpretation: İ.D., D.T., Writing: İ.D., D.T.

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