JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1351577
J Contemp Med 2023;13(5):939-948

Original Article / Orijinal Araştırma

Evaluation of Response to Stereotactic Radiosurgery and Survival Outcomes in Patients with Brain Metastases from Gastrointestinal Cancers

Gastrointestinal Kanserlerden Gelişen Beyin Metastazı Olan Hastalarda Stereotaktik Radyocerrahiye Yanıtın ve Sağkalım Sonuçlarının Değerlendirilmesi

Ela Delikgoz Soykut[1], Eylem Odabaşı[1], Serdar Şenol[2], Salih Buğra Yılmaz[3], Hatice Tataroğlu[1], Ahmet Baran[4]

[1]Samsun Training and Research Hospital, Department of Radiation Oncology, Samsun, Türkiye
[2]Samsun Training and Research Hospital, Department of Gastroenterological Surgery, Samsun, Türkiye
[3]Samsun Training and Research Hospital, Department of Neurosurgery, Samsun, Türkiye
[4]Samsun Training and Research Hospital, Department of Medical Oncology, Samsun, Türkiye

Abstract

Aim: Gastrointestinal cancers rarely metastasize to the brain and constitute 4-8% of all brain metastases (BM). Survival is generally poor for BM from gastrointestinal cancers and stereotactic radiosurgery (SRS) is frequently used in its management. Since the data are still insufficient due to their rare presentation, we aim to analyze the clinical results of patients who underwent SRS for BM due to gastrointestinal cancers.

Material and Method: We retrospectively reviewed patients with BM from gastrointestinal cancers who received robotic SRS with CyberKnife at our institute from October 2013 to December 2022. Clinical characteristics and treatment outcomes were recorded. Study endpoints were local control rates, distant brain control rates, and overall survival (OS).

Results: A total of 61 BM were detected in 42 patients. The median clinical follow-up time was 7 (0.5-36) months. Nine lesions progressed in the irradiated area, 14 new lesions were observed outside the irradiated area. The local control rate was 85.1% and the distant brain control rate was 77%. The median OS was 8 months; 12-month and 24-month OS were 31.6% and 10.5%, respectively. Patients with high performance status had better OS (p=0.016). The prognostic scoring scales recursive partitioning analysis (RPA) and graded prognostic assessment scores for gastrointestinal cancers (GI-GPA) were both associated with OS, in univariate analysis (p=0.049, p=0.002). Multivariate analysis found a significant association between GI-GPA classes and OS (p=0.011).

Conclusion: We obtained comparable results in terms of local control, distant brain control and OS in this challenging patient population. The use of GI-GPA prognostic scoring scales in routine practice will guide the selection of the most appropriate patient for SRS.

Keywords: Brain metastases, gastrointestinal cancer, prognosis, stereotactic radiosurgery

Öz

Amaç: Gastrointestinal kanserler nadiren beyne metastaz yapar ve tüm beyin metastazlarının (BM) %4-8'ini oluşturur. Gastrointestinal kanserlerden gelişen BM için prognoz genellikle kötüdür ve tedavisinde stereotaktik radyocerrahi (SRS) sıklıkla kullanılır. Nadir prezentasyonları nedeniyle veriler hala yetersiz olduğundan, gastrointestinal kanserlerden gelişen BM için SRS uygulanan hastaların klinik sonuçlarını analiz etmeyi amaçladık.

Gereç ve Yöntem: Ekim 2013'ten Aralık 2022'ye kadar enstitümüzde CyberKnife ile robotik SRS alan gastrointestinal kanserlerden gelişen BM'li hastaları retrospektif olarak incelendi. Klinik özellikler ve tedavi sonuçları kaydedildi. Çalışma sonlanım noktaları, yerel kontrol oranları, uzak beyin kontrol oranları ve genel sağkalım (OS) idi.

Bulgular: 42 hastada toplam 61 BM tespit edildi. Ortalama klinik takip süresi 7 (0,5-36) aydı. Işınlanan sahada 9 lezyonda progresyon izlenirken, ışınlanan alan dışında 14 yeni lezyon gözlendi. Lokal kontrol oranı %85,1, uzak beyin kontrol oranı ise %77 olarak saptandı. Medyan OS 8 aydı; 12 aylık ve 24 aylık OS sırasıyla %31,6 ve %10,5 idi. Performans durumu yüksek olan hastaların OS'si daha iyiydi (p=0,016). Tek değişkenli analizde, prognostik skorlama ölçeklerinden recursive partitioning analysis (RPA) ve gastrointestinal kansrler için graded prognostic assessment (GI-GPA) her ikisi de OS ile ilişkiliydi (p=0,049, p=0,002). Çok değişkenli analizde, GI-GPA sınıfları ile OS arasında anlamlı bir ilişki bulundu (p=0,011).

Sonuç: Bu zorlu hasta popülasyonunda lokal kontrol, uzak beyin kontrolü ve OS açısından karşılaştırılabilir sonuçlar elde ettik. GI-GPA prognostik skorlama ölçeklerinin rutin uygulamada kullanılması, SRS için en uygun hastanın seçimine yol gösterecektir.

Anahtar Kelimeler: Beyin metastazı, gastrointestinal kanser, prognoz, stereotaktik radyocerrahi

Corresponding *(İletişim)*: Ela Delikgoz Soykut, Samsun Training and Research Hospital, Department of Radiation Oncology, Samsun, Türkiye
E-mail *(E-posta)*: eladelikgoz@gmail.com
Received *(Geliş Tarihi)*: 28.08.2023 **Accepted *(Kabul Tarihi)*:** 26.09.2023

INTRODUCTION

Gastrointestinal cancers rarely metastasize to the brain and constitute 4-8% of all brain metastases (BM).[1] Esophageal and gastric cancers cause BM at a lower rate than colorectal cancers.[2] Especially in colorectal cancers, the increase in the follow-up period due to the prolongation of survival is associated with the development of metastatic disease. At the same time, the more widespread use of imaging methods allows for more frequent detection of BM.

Survival is quite poor when BM develops in gastrointestinal cancers, and a median survival of about 6 months has been reported in many studies.[2,3] Although there are no optimal treatment recommendations with a high level of evidence for BM associated with gastrointestinal cancers, treatment options such as surgery, whole brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS) are applied.[3,4] The choice of treatment is made by considering several factors, such as the condition of the disease, the response to previous treatments, the presence of extracranial metastases, the number and location of BM, and the performance status.[1,5] Surgical treatment cannot be applied frequently due to extensive extracranial disease, advanced age, or decreased performance status. In this situation, radiotherapy remains the most common treatment method. WBRT is a radiotherapy technique that has traditionally been used for BM for many years, and today it is more commonly preferred in patients with widespread disease, leptomeningeal involvement, and low performance scores. Over the years, technological developments have enabled the development of modern radiotherapy techniques, and in this context, WBRT has largely left its place to SRS techniques with the accumulating evidence.[6,7]

SRS has advantages such as having fewer neurological side effects, shortening the treatment time, and increasing patient compliance compared to WBRT. In addition, it does not require invasive procedures compared to surgery. The most important oncological contribution of SRS is that it increases local tumor control.[6,7] Studies evaluating the outcome of SRS include reviews involving lung and breast cancer patients with an increased incidence of BM.[6,7] Since the incidence of BM due to gastrointestinal cancers is much lower, SRS results in this group of patients are still not sufficient and are often based on retrospective data.[2-4,8] In a retrospective series in which different treatment modalities were evaluated, it was reported that survival times increased from 4 months to 11.1 months with SRS compared to WBRT in patients with gastrointestinal cancer.[4] This survival contribution following SRS is quite significant, as the expected median survival times after BM development are approximately 6 months.[2-4,8] Since the data are still insufficient due to the rarity of BM due to gastrointestinal cancers, we aim to analyze the clinical results of patients who underwent SRS in our clinic since 2013. The purpose of this retrospective study was to determine local and distant intracranial control rates and survival rates and to determine prognostic factors associated with clinical outcomes in patients who underwent SRS with a diagnosis of BM due to gastrointestinal cancers.

MATERIAL AND METHOD

Patient Characteristics

The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (Date: 2023, Decision No: 15/4). Because the study was designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[9]

We retrospectively reviewed patients with BM from gastrointestinal cancers who received robotic SRS with the CyberKnife device at the Radiation Oncology Clinic of Samsun Training and Research Hospital from October 2013 to December 2022.

Patients with histopathologically confirmed gastrointestinal cancer (esophagus, gastric, liver, biliary tract, pancreas, small bowel, colon, rectum, and anal canal) as the primary and with BM according to imaging studies were included. In addition, patients with BM whose primary tumor location was unknown but histopathologically demonstrated to have spread from a gastrointestinal primary after surgery for BM were also included in the study. Patients who underwent WBRT alone or surgery alone were not included in the study.

The analysis was extracted utilizing the medical records system. Clinical data, including patient age, gender, Karnofsky performance status (KPS), date of initial diagnosis, stage of initial diagnosis, location of initial diagnosis, date of BM diagnosis, location of BM, size and volume of BM, number of BM, recursive partitioning analysis (RPA) scores,[10] graded prognostic assessment (GI-GPA) scores for gastrointestinal cancers,[11] KRAS status, HER-2 status, presence of extracranial metastases, whether the primary disease is under control, and treatment data, including chemotherapy, surgery, and radiotherapy were collected. The biologically effective dose (BED) calculated using $a/\beta = 10$ (BED10) and $a/\beta = 3$ (BED3) for tumor effects and normal tissue effects.

Treatment Planning and Delivery

SRS treatment planning and delivery was done on the CyberKnife® (Accuray, Sunnyvale, USA) Robotic SRS system. For immobilization, a custom-made thermoplastic mask was fitted. Thin-slice computed tomography images and contrast-enhanced magnetic resonance imaging (MRI) were acquired in the supine position. Image fusion was performed for accurate tumor delineation. The gross target

volume (GTV) was defined as the contrast-enhancing lesion, the planning target volume (PTV) was defined as 0-1 mm and 2 mm isotropic expansion from GTV for SRS and cavity SRS. The software Multiplan v4.5 (MultiPlan, Inc., New York, USA) was used for treatment planning. BM with a large target volume and located close to the brainstem or optic chiasm were treated with fractionated treatments; otherwise, single fractions were used.

Follow up

The clinical assessment was evaluated by neurological examination and imaging. The first clinical evaluation after treatment was made at the visit two weeks later. Follow-up MRI studies were usually first obtained within 1 to 2 months after SRS, then performed at 2-month intervals. The Response Evaluation Criteria in Solid Tumors (RECIST) [12] was used for response assessment. Stable disease, partial or complete response according to MRI findings was accepted as local control. An increase in the size of the radiographically enhanced lesion in the irradiated area was accepted as local progression, and new enhancement outside the irradiated area was considered distant brain failure.

Endpoints and Statistical Analysis

Local and distant brain control rates were the primary endpoints of the study, and overall survival (OS) was the secondary endpoint. OS was set from the day of BM diagnosis to the date of death or loss to follow-up. The radiographic follow-up duration was defined as the time from the date of SRS to the last date of imaging follow-up, and the clinical follow-up duration was defined as the time from the date of SRS to the last date of follow-up.

Baseline patient and tumor variables (age, gender, size, volume of BM, treatment parameters, dose, etc.) were analyzed for descriptive characteristics (mean, median, percentage, etc.). The Fisher exact test, or the chi-square test, was applied to analyze intergroup differences. The independent t-test was used when the datasets were normally distributed; otherwise, datasets were compared by the Kruskal-Wallis test. Kaplan-Meier estimates were used for the calculation of local control rates, distant brain control rates, and OS. The log-rank test was used to evaluate the associations of local control rates, distant brain control rates, and OS with various clinical factors. The Cox proportional-hazards model was used for univariate and multivariate analyses. A p value of less than 0.05 was considered to indicate a statistically significant difference. SPSS v25 (SPSS Inc., Chicago, USA) statistical program was used.

RESULTS

Table 1 provides the clinical and treatment characteristics of the study cohort. A total of 61 BM developed from gastrointestinal cancer were identified in 42 patients, including 3 esophageal cancers, 9 gastric cancers, 1 biliary cancer, 15 colon cancers, and 14 rectal cancers. The median patient age at diagnosis of BM was 63 (41-77) years. In 40 (95.2%) of the patients, adenocarcinoma constituted the majority of the tumor histology. Fourteen patients were analyzed for mutations in KRAS (10 wild-type, 4 mutated), and seven patients were analyzed for HER-2 receptor status (2 positive, 5 negative). Eighteen (42.8%) of the patients were stage 4 at the time of initial diagnosis, and four (9.5%) of them were diagnosed with BM. Five (11.9%) patients underwent open neurosurgical resection before SRS. Prior to SRS, WBRT was given to 20 patients (47.6%), with a median dose of 30 Gy (20-37.5). For radiosurgery, a median of 20 Gy (15-24) was applied to 38 BM in 1 fraction, and a median of 24 Gy (16-30) was applied to 23 BM in a median of 3 (2-5) fractions. Regarding patient and treatment characteristics by the location of primary diagnosis, there was no difference between upper gastrointestinal and lower gastrointestinal malignancies (**Table 1**).

The median clinical follow-up time was 7 (0.5-36) months. MRI could not be performed because 14 patients died in the first 3 months after SRS, and only physical examination records of these patients were available. Apart from these, the median radiographic follow-up period was 5 months (1-23) in 27 patients who were followed up with MRI after SRS. In the irradiated area, nine (14.8%) lesions progressed in a median of 7 months (4-20). Outside the irradiated area, 14 (23%) new lesions were observed at a median of 3 months (2-11). SRS (2nd series SRS in 6 patients, 3rd series SRS in 3 patients, and 4th series SRS in 1 patient) was applied to the new lesions detected during the follow-up period. Salvage WBRT was applied to 3 patients with multiple BM in a median of 10 months (9-15), and 2 of these patients received 3rd series SRS before WBRT.

The local control rate was 85.1% at the last follow-up, the 6-month, 12-month, and 24-month, local control rates were 94.9%, 71.6%, and 61.4%, respectively. There was no difference in the local control ratio in terms of patient, tumor, and treatment characteristics (**Table 2**). The distant brain control rate was 77% at the last follow-up; the 6-month, 12-month, and 24-month distant brain control rates were 78.6%, 48.9%, and 48.9%, respectively. There was no difference in the distant brain control ratio in terms of patient, tumor, and treatment characteristics, except for the location of the primary tumor (**Table 2**). According to the location of the primary tumor, the 12-month local control rate for upper and lower gastrointestinal cancers was 63.8% and 85.7%, respectively, but there was no statistically significant difference (**Figure 1a**). In contrast, the 12-month distant brain control rate was 93.8% and 27.6% for upper and lower gastrointestinal cancers, with a statistically significant difference (p=0.018, HR: 1.50, 95%: CI 8.05-13.54) (**Figure 1b**). Multivariate analysis found no association with primary tumor location for distant brain control (p=0.059, HR: 7.16, 95% CI: 0.92-55.49).

Table 1. Clinical and treatment characteristics of patients with brain metastases from upper and lower gastrointestinal cancers

Characteristic	Upper GI (n, %) (mean+/-SD)	Lower GI (n, %) (mean+/-SD)	p
Age			
<60	5 (38.5)	8 (27.6)	0.495
≥60	8 (61.5)	21 (72.4)	
Gender			
Female	4 (30.8)	13 (44.8)	0.391
Male	9 (69.2)	16 (55.2)	
KPS			
90-100	8 (61.5)	9 (31)	0.097
70-80	2 (15.4)	8 (27.6)	
60	3 (23.1)	12 (41.4)	
RPA			
I	5 (38.5)	3 (10.3)	0.057
II	5 (38.5)	14 (48.3)	
III	3 (23.1)	12 (41.4)	
GI-GPA			
0-1.0	1 (7.7)	7 (24.1)	
1.5-2.0	6 (46.2)	13 (44.8)	0.080
2.5-3.0	2 (15.4)	7 (24.1)	
3.5-4.0	4 (30.8)	2 (6.9)	
Stage of primary diagnosis			
Stage 2-3	7 (53.8)	17 (58.6)	0.773
Stage 4	6 (46.2)	12 (41.4)	
Controlled primary			
Yes	6 (46.2)	18 (62.1)	0.335
No	7 (53.8)	11 (37.9)	
Extracranial metastases			
Yes	9 (69.2)	22 (75.9)	0.713
No	4 (30.8)	7 (24.1)	
Number of brain metastases			
1	6 (46.2)	15 (51.7)	0.739
≥2	7 (53.8)	14 (48.3)	
Size of brain metastases (cm)			
<2 cm	5 (38.5)	11 (37.9)	0.618
≥2 cm	8 (61.5)	18 (62.9)	
Volume of brain metastases (cc)			
<10 cc	11 (84.6)	20 (69)	0.453
≥10 cc	2 (15.4)	9 (31)	
Surgery for brain metastases			
Yes	2 (15.4)	3 (10.3)	0.637
No	11 (84.6)	26 (89.7)	
WBRT			
Yes	5 (38.5)	15 (51.7)	0.426
No	8 (61.5)	14 (48.3)	
SRS			
1 fx	6 (46.2)	15 (51.7)	0.739
2-5 fx	7 (53.8)	14 (48.3)	
SRS Dmax (cGy)	2405+/-443	2518+/-464	0.517
Coverage (%)			
<98.5	5 (38.5)	14 (48.3)	0.524
≥98.5	8 (61.5)	15 (51.7)	
HI	1.18+/-0.06	1.18+/-0.045	0.990
CI	1.38+/-0.26	1.29+/-0.18	0.190
nCI	1.40+/-0.26	1.32+/-0.19	0.265
BED10			
<40	5 (38.5)	5 (17.2)	0.238
≥40	8 (61.5)	24 (82.8)	
BED3			
<90	6 (46.2)	9 (31)	0.488
≥90	7 (53.8)	20 (69)	
Chemotherapy			
Yes	13 (100)	28 (96.6)	0.690
No	0 (0)	1 (3.4)	
Targeted agent therapy			
Yes	2 (15.4)	17 (58.6)	0.091
No	11 (84.6)	12 (41.4)	

BED: Biologically effective dose, CI: Conformity index, GI: Gastrointestinal, GPA: Graded prognostic assessment, HI: Homogeneity index, KPS: Karnofsky performance score, nCI: New conformity index, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

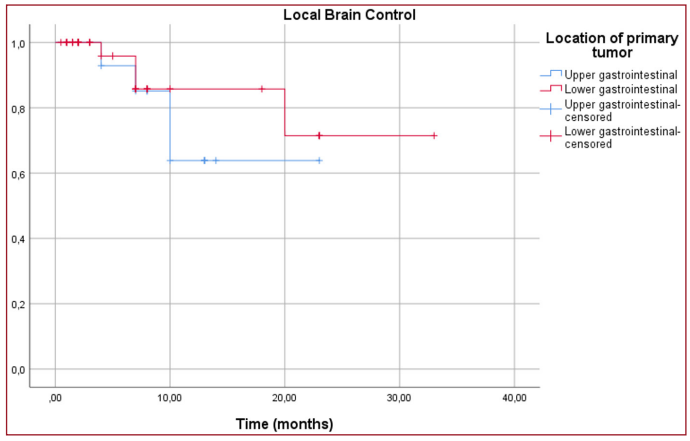

Figure 1a. Kaplan-Meier graph of local control rate according to the location of the primary tumor.

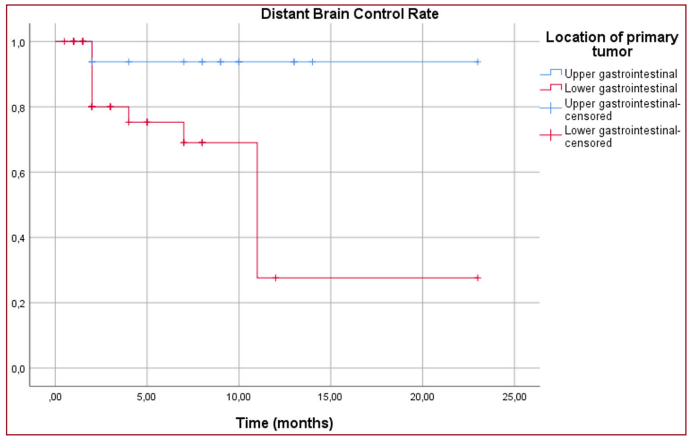

Figure 1b. Kaplan-Meier graph of distant brain control rate according to the location of the primary tumor.

Of the 42 patients included in the study, only four were alive at the last follow-up. The median OS was 8 months (HR: 2.51, 95% CI: 3.07-12.92), and the 6-month, 12-month, and 24-month OS were 57%, 31.6%, and 10.5%, respectively (**Figure 2a**). According to the location of the primary tumor, the 12-month OS for upper and lower gastrointestinal cancers was 50% and 20.9%, respectively, but there was no statistically significant difference (p=0.567, **Table 3**) (**Figure 2b**). Patients with high performance status had better OS than patients with low performance status (p=0.016, **Table 3**) (**Figure 2c**). The prognostic scoring scales RPA and GI-GPA were both associated with OS (p=0.049, p=0.002, **Table 3**) (**Figures 2d**, **2e**). The median OS was longer in patients with a controlled primary tumor and those undergoing surgery for BM, but it was not statistically significant (p=0.296, p=0.814, **Table 3**). Since all but one patient received chemotherapy at some point in their treatment period, its effect on OS could not be evaluated statistically. In terms of those receiving targeted therapy, the OS contribution could not be shown statistically (p=0.604, **Table 3**). Multivariate analysis found a significant association between GI-GPA classes (except GPA 0 to 1.0 vs. 1.5 to 2.0) and OS (p=0.011, HR: 0.10, 95% CI: 0.01-0.58).

Table 2. Univariate analysis for factors influencing Local control and Distant brain control

Characteristic	Local control rate HR (CI 95%)	p	Distant brain control rate HR (CI 95%)	p
Age <60 vs ≥60	0.72 (0.19-2.73)	0.635	0.70 (0.23-2.09)	0.525
Gender Female vs male	1.20 (0.31-4.53)	0.788	0.81 (0.27-2.37)	0.706
KPS 90-100 vs 70-80 vs 60	0.80 (0.45-3.15)	0.530	0.95 (0.33-4.12)	0.381
Primary disease Upper GI vs lower GI	0.46 (0.10-2.07)	0.314	1.50 (8.05-13.54)	0.018
RPA I vs II vs III	2.21 (0.74-6.60)	0.152	1.74 (0.74-4.07)	0.198
GI-GPA 0-1.0 vs 1.5-2.0 vs 2.5-3.0 vs 3.5-4.0	0.68 (0.25-2.55)	0.711	1.30 (0.56-2.96)	0.534
Stage of primary diagnosis Stage 2-3 vs stage 4	1.74 (0.46-6.54)	0.407	2.08 (0.72-6.05)	0.175
Controlled primary Yes vs no	0.16 (0.02-1.34)	0.093	1.69 (0.59-4.84)	0.327
Extracranial metastases Yes vs no	0.96 (0.23-3.99)	0.963	0.64 (0.17-2.33)	0.505
KRAS status + vs -	1.39 (0.57-3.33)	0.462	0.64 (0.32-1.28)	0.215
Her 2 status + vs -	1.14 (0.32-3.77)	0.874	0.69 (0.27-1.24)	0.435
Number of brain metastases 1 vs ≥2	0.87 (0.21-3.49)	0.846	1.55 (0.47-5.07)	0.461
Size of brain metastases (cm) <2 cm vs ≥2 cm	0.84 (0.22-3.18)	0.803	0.85 (0.29-2.45)	0.764
Volume of brain metastases (cc) <10 cc vs ≥10 cc	0.83 (0.17-4.04)	0.821	1.49 (0.49-4.48)	0.473
Surgery for brain metastases Yes vs no	0.57 (0.07-4.69)	0.605	23.47 (0.00-66.77)	0.437
WBRT Yes vs no	4.07 (0.83-19.94)	0.083	1.64 (0.56-4.79)	0.362
SRS 1 fx vs 2-5 fx	0.87 (0.23-3.28)	0.848	1.58 (0.54-4.59)	0.396
Coverage (%) <98.5 vs ≥98.5	0.85 (0.22-3.19)	0.815	0.75 (0.49-4.48)	0.602
BED10 <40 vs ≥40	1.20 (0.14-9.84)	0.862	28.82 (0.05-156.84)	0.296
BED3 <90 vs ≥90	0.74 (0.18-2.97)	0.674	1.00 (0.31-3.21)	0.999
Targeted agent therapy Yes vs no	1.12 (0.24-5.08)	0.879	0.75 (0.24-2.32)	0.620

BED: Biologically effective dose, CI: Confidence interval, CI: Conformity index, GI: Gastrointestinal, GPA: Graded prognostic assessment, HI: Homogeneity index, HR: Hazard Ratio; KPS: Karnofsky performance score, nCI: New conformity index, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

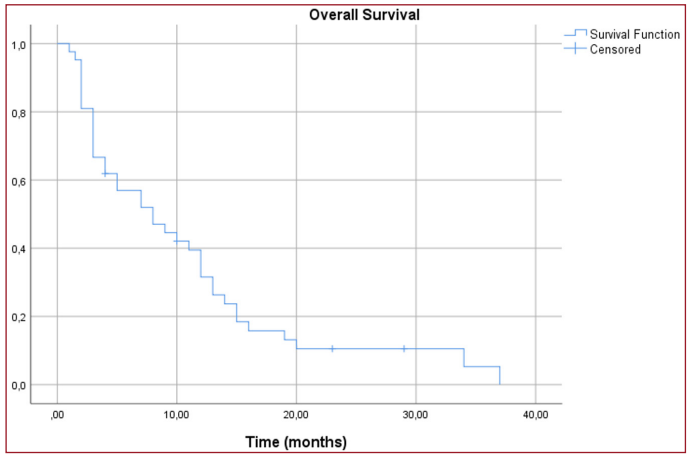

Figure 2a. Kaplan-Meier graph of OS.

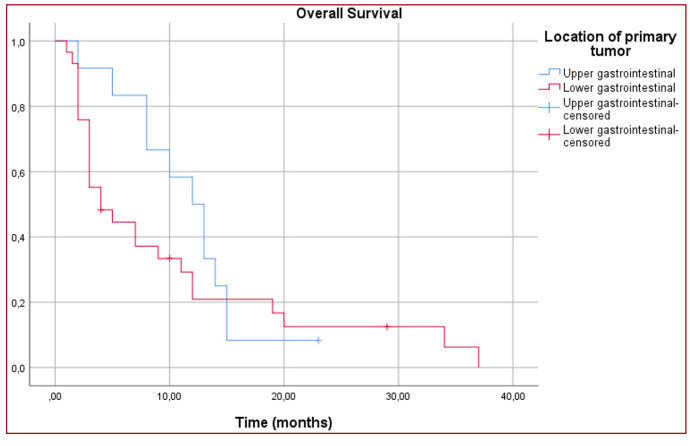

Figure 2b. Kaplan-Meier graph of OS according to the location of the primary tumor.

Table 3. Univariate analysis for factors influencing OS

Characteristic	6-m	12-m	24-m	Median OS	HR (CI 95%)	p
Age						
<60	61.5	46.2	0	12	3.59 (4.95-19.04)	0.369
≥60	47.6	24.7	12.4	7	2.04 (2.980-11.01)	
Gender						
Female	64.7	40.3	13.4	9	3.97 (1.21-16.78)	0.353
Male	51.4	25.7	8.2	8	2.35 (3.39-12.60)	
KPS						
90-100	81.9	56.7	18.9	13	2.95 (7.20-18.79)	0.016
70-80	30	20	0	4	1.05 (1.93-6.06)	
60	40	8.9	0	3	0.47 (2.07-3.93)	
RPA						
I	75	50	0	12	1.88 (8.30-15.69)	0.049
II	51.3	34.2	17.1	10	4.10 (1.94-18.05)	
III	40	8.2	0	3	0.47 (2.07-3.93)	
GI-GPA						
0-1.0	37.5	0	0	3	0.68 (1.65-4.34)	
1.5-2.0	36.8	18.4	0	5	1.07 (2.89-7.10)	0.002
2.5-3.0	64.8	38.9	38.9	13	2.67 (7.76-18.23)	
3.5-4.0	83.3	66.7	16.7	15	3.67 (7.79-22.20)	
Primary disease						
Upper GI	83.3	50	0	12	1.73 (8.60-15.39)	0.567
Lower GI	44.6	20.9	12.5	4	1.74 (0.57-7.42)	
Stage of primary diagnosis						
2-3	62.2	29.6	0	9	1.75 (5.56-12.43)	0.823
4	38.9	33.3	11	5	1.05 (2.93-7.06)	
Controlled primary						
Yes	57.8	34.2	14.7	10	3.01 (4.09-15.90)	0.296
No	44.4	27.8	0	5	3.18 (0.00-11.23)	
Extracranial metastases						
Yes	47.8	37	7.4	7	3.31 (0.50-13.49)	0.922
No	63.6	18.2	0	8	1.65 (4.76-11.23)	
Number of brain metastases						
1	41.9	36.7	10.5	5	2.74 (0.00-10.38)	0.983
≥2	66.7	26.8	5.4	9	2.28 (4.51-13.48)	
Size of brain metastases						
<2 cm	50	37.5	6.3	9	7.0 (0.00-22.72)	0.997
≥2 cm	57.2	36.3	9.1	7	1.82 (3.42-10.58)	
Volume of brain metastases (cc)						
<10 cc	48.4	28.2	5.3	7	1.94 (3.18-10.81)	0.341
≥10 cc	61.4	40.9	10.2	12	3.81 (4.53-19.46)	
Surgery for brain metastases						
Yes	60	40	0	12	4.38 (3.41-20.58)	0.814
No	53.8	30.5	12.2	7	2.43 (2.22-11.78)	
WBRT						
Yes	55	30	15	8	2.23 (3.61-12.38)	0.422
No	49.2	33.8	0	7	2.92 (1.26-12.73)	
SRS						
1 fx	42.9	28.6	0	4	1.90 (0.26-3.73)	0.183
2-5 fx	61	34.3	17.1	9	2.12 (4.83-13.16)	
BED10						
<40	40	20	0	5	3.16 (0.00-11.19)	0.157
≥40	59.2	35.4	14.2	8	3.21 (1.70-14.29)	
BED3						
<90	53.3	20	0	8	1.89 (4.28-11.71)	0.444
≥90	59.3	38.8	12.9	10	3.80 (2.54-17.45)	
Targeted agent therapy						
Yes	52.6	24.6	0	7	2.86 (1.37-12.62)	0.604
No	69.2	26	17.3	10	3.30 (3.52-16.47)	

BED: Biologically effective dose, CI: Confidence interval, GI: Gastrointestinal, GPA: Graded prognostic assessment, HR: Hazard Ratio; OS: Overall survival, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

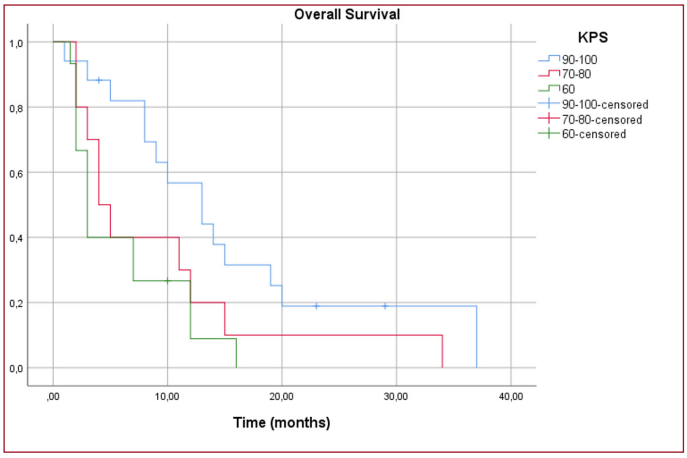

Figure 2c. Kaplan-Meier graph of OS according to KPS.

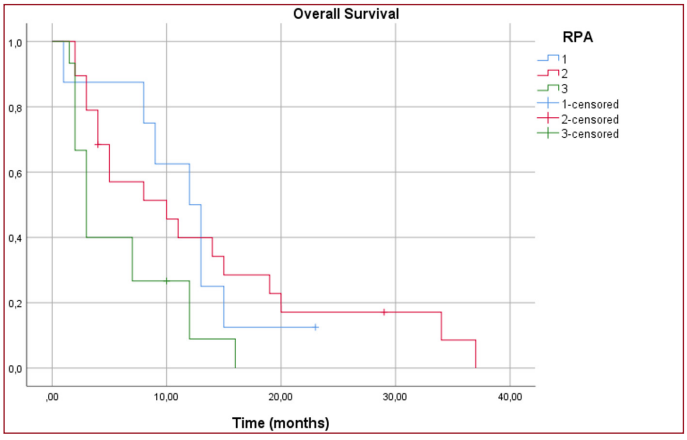

Figure 2d. Kaplan-Meier graph of OS according to RPA.

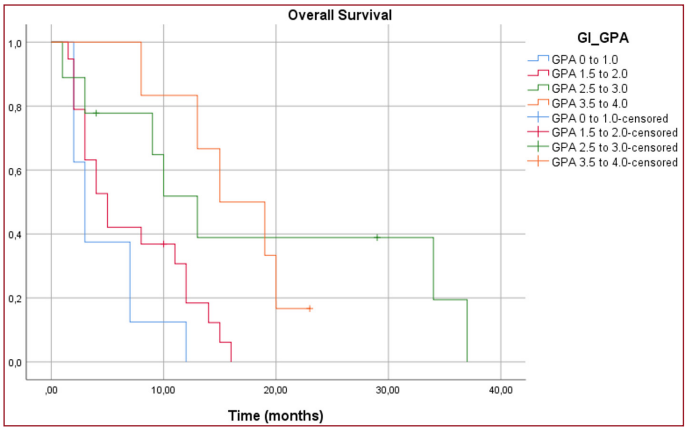

Figure 2e. Kaplan-Meier graph of OS according to GI-GPA.

DISCUSSION

In a cohort of patients with BM from gastrointestinal cancers treated with SRS, we retrospectively evaluated the clinical outcomes of SRS. We identified two main findings: First, comparable results were obtained in terms of the local control rate and the distant brain control rate. Second, the performance status and prognostic scoring scales RPA and GI-GPA were associated with OS.

The outcomes of SRS are typically based on the findings of retrospective series due to the rarity of BM in gastrointestinal malignancies.[2-4,13-15] Tumor control is a crucial component of SRS for the treatment of BM. To our knowledge, local tumor control rates of 64% to 94% have been reported to be achieved with SRS for gastrointestinal BM. In a study in which 40 patients underwent SRS in 118 BM from gastrointestinal cancer, a local control rate of 91% was reported in 25 patients with radiological follow-up.[13] Another study showed a local control rate of 94.1% after SRS in 261 BM from 86 patients.[2] In the series of Paudel et al.[14], which included 53 patients and 148 BM, the 6-month and 12-month local control rates were determined as 74.33% and 57.21%, respectively. Despite the limited number of patients and BM treated in these series, excellent outcomes in terms of local control rates were found. In contrast, series with lower local control rates are also seen. For instance, in the series that included 21 patients with 28 BM, the local control rate was 64.3%, and the 6-month local control rate was 47% in patients with radiographic follow-up.[15] In accordance with previous research that also demonstrated encouraging local control rates, we observed that the local control rate in our study was 85.1%, and the 12-month local control rate was 71.6%.

According to previous investigations, there are some criteria that are assumed to predict local control.[2,15-17] The treatment dose is one of the parameters that has been demonstrated to increase local control. Triffletti et al.[2] reported that a margin dose ≥20 Gy had a significant effect on local control in their series of Gamma Knife SRS. In the study of Shangvi et al.[15], treatment dose was defined as a factor affecting the development of distant brain metastasis without influencing local control. However, the Italian study, which examined 262 BM from 185 colorectal patients and was published in 2020, failed to identify any factors affecting local control.[16] Preliminary results of a multicenter study involving 263 patients with 543 BM showed improved local brain control with a high performance score, a lower patient age, and a small tumor diameter.[17] In this series, although the treatment dose was effective for local control in univariate analysis, it lost its importance in multivariate analysis. As can be observed, factors determined to be predictive of local control in one cohort may be inconsequential in another. The rarity of BM associated with gastrointestinal cancers renders studies inconclusive and yields inconsistent findings. In our study, a factor related to local control, such as the Italian multicenter study, could not be determined.

Although local control rates in BM with SRS are quite good, distant brain control remains a challenging issue. In a series of 53 patients with a median follow-up of 6 months, it was reported that distant BM developed in almost half of the patients (26 patients) at the final follow-up.[14] In another series of 33 patients with a median radiographic follow-up of 3.9 months, the rate of distant brain control

was reported as 46.4% at the last control.[15] In the Italian multicenter study, distant BM developed in 71 (38.4%) patients in a median of 3 months (1-82), and the 6-month, 12-month, and 24-month distant brain control rates were 66.4%, 55.3%, and 47.5%, respectively.[16] In our study, distant brain control was 77% at the last follow-up, with a median 5-month radiographic follow-up. The 6-month, 12-month, and 24-month distant brain control rates were 78.6%, 48.9%, and 48.9%, respectively. As such, it appears that we have comparable results in terms of distant brain control.

Increasing number of BM and advanced patient age have been identified as factors that reduce distant brain control.[18] Half of the patients included in our study had single BM; there was no difference in distant brain control compared to patients with multiple BMs. On the other hand, advanced patient age was not found to be a factor affecting distant brain control in our study. In the study evaluating BM from 802 gastrointestinal cancers, no difference was found in terms of upper and lower gastric cancers after SRS.[19] In our study, it was determined that distant brain control was better in upper gastrointestinal localized patients, but this difference did not persist in the multivariate analysis.

Survival is generally dismal for BM from gastrointestinal cancers, with several studies reporting a median survival of approximately 6 months.[2-4,8,13,16,19,20] The median survival was 5 months in the series of Hagesava et al.[20], which included 39 patients, and 6.7 months in the series of Da Silva et al.[13], which included a similar number of patients. Page et al.[8] reported a median survival of 7.1 months in 62 patients. Two multicenter studies with larger numbers of patients did not yield different results in terms of OS. One of them, the Italian study, reported median, 6-month and 12-month OS rates of 7 months, 52.7%, and 33%.[16] In the other, the median survival was 5.7 months, and the 6-month and 12-month OS rates were 46.3% and 21.9%, respectively.[19] In our study, the median OS, 6-month OS, and 12-month OS were 8 months, 57%, and 31.6%, respectively. The survival results in our study were consistent with previous studies.

In our study, we categorized the patients as having upper and lower gastrointestinal cancer to evaluate whether the primary tumor location had an effect on the results. Although the median survival times we found for upper and lower gastrointestinal tumors were different, they were not statistically significant. To our knowledge, studies often included either studies examining all gastrointestinal cancers together or colorectal cancers, as they were more common than other gastrointestinal cancers. We found two retrospective series in which SRS was applied only for the diagnosis of gastric cancer. The number of patients in both series was quite small, with median OS after SRS of 17 months in 11 patients and 10 months in 15 patients.[21,22] In another study, a median OS of 16 months was reported in 21 patients with esophageal cancer.[23] In larger series involving 93 and 116 colorectal cancer patients, the median OS was found to be 7 and 10.3 months, respectively.[24,25] In the study of Yamomota et al.[19], which has the highest number of patients on this subject, it is thought that those with lower gastrointestinal cancer had a longer survival than those with upper gastrointestinal cancer (5.9 months vs. 4.8 months), but this finding was not statistically significant. In our study, we found that upper and lower gastrointestinal cancers were similar in terms of patient and treatment parameters; we did not detect a statistically significant difference between the two groups.

When previous research was analyzed, it was discovered that performance status is one of the most important determinants of survival.[2,19,23,24] This finding was corroborated by both small-patient studies and multicenter studies. In addition, controlled primary cancer and the absence of extracerebral metastases were variables found in previous studies that were significantly associated with OS.[8,19,24] Also, several studies have shown improved survival with single BM and resection for BM.[2,19,24] In our study, only performance status was found to be a factor influencing OS in univariate analysis, but this effect did not exist in multivariate analysis.

In fact, the performance score was the sole essential prognostic baseline component of the GI-GPA. Patient age, the number of BM, and the presence or absence of extracranial metastases are the parameters used in the algorithm to calculate GI-GPA along with KPS.[11] It is not unexpected that the aforementioned studies show that these parameters are prognostic for survival, even when evaluated separately. However, it is clearly known that not all parameters have a prognostic effect in terms of survival in every study.[2,15,24] Since it is more difficult to predict the prognosis with a single parameter, more accurate and reliable information can be obtained with GI-GPA.

The requirement to establish a prognosis led to the development of prognostic risk scoring. Historically, RPA has been defined and long used for BM.[10] For instance, Park et al.[22] showed that RPA II class was associated with prolonged survival. But new prognostic classifications have become necessary in the era of SRS, as there are aggregations among RPA classes, especially in RPA II. The GPA developed in this context was further modified, and disease-specific subclassifications were created.[11] In this regard, a retrospective cohort study of 802 patients was designed for GI-GPA validation.[19] Median survival times for the GI-GPA subgroups (1, 2, 3, and 4) were reported as 3.5 vs. 6.1 vs. 7.7 vs. 11 months, respectively. However, there was no significant difference in survival between subgroups 2 and 3. In our study, survival rates of 3 vs. 5 vs. 13 vs. 15 months were determined for the GI-

GPA subgroups, respectively. In our cohort, the survival difference between subgroups 1 and 2 was not significant (p=0.186). Although the number of our patients was quite low compared to the validation study, GI-GPA efficiency could still be demonstrated. We consider that GI-GPA retains its predictive effect on survival regardless of the size of the cohort.

Finally, we noted KRAS status and HER-2 status while recording patient characteristics. There were not many patients whose data, including receptor status, we could access. We could not detect a significant difference with the available data. However, in the cohort in which the results of SRS in colorectal cancers were published recently, it was reported that the survival of those with KRAS mutations worsened, and this issue was highlighted.[25]

There were several limitations to the current series. First of all, the retrospective design with the small sample size from a single institution was subject to biases. Secondly, given the sparsity of the cases, there was significant heterogeneity in the patient population. Our series may not have been able to provide frequencies to generalize since the number of patients was small and it included all gastrointestinal cancers. Lastly, the fact that KRAS status and HER-2 status were unknown in all patients is another limitation of our study.

CONCLUSION

In conclusion, BM from gastrointestinal cancer is infrequent and has a poor prognosis. In this challenging patient population, our SRS treatment outcomes in terms of local control, distant brain control, and survival are comparable to those of previous research. In routine practice, using GI-GPA prognostic scoring scales as well as the patient's performance status will be a guide to selecting the most suitable patient for SRS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (Date: 2023, Decision No: 15/4).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Patchell RA. The management of brain metastases. Cancer Treat Rev. 2003;29(6):533-40.
2. Trifiletti DM, Patel N, Lee CC, Romano AM, Sheehan JP. Stereotactic radiosurgery in the treatment of brain metastases from gastrointestinal primaries. J Neurooncol. 2015;124(3):439-46.
3. Ghidini M, Petrelli F, Hahne JC, et al. Clinical outcome and molecular characterization of brain metastases from esophageal and gastric cancer: a systematic review. Med Oncol. 2017;34(4):62.
4. Lin L, Zhao CH, Ge FJ, et al. Patients with brain metastases derived from gastrointestinal cancer: clinical characteristics and prognostic factors. Clin Transl Oncol. 2016;18(1):93-8.
5. Mjahed RB, Astaras C, Roth A, Koessler T. Where Are We Now and Where Might We Be Headed in Understanding and Managing Brain Metastases in Colorectal Cancer Patients?. Curr Treat Options Oncol. 2022;23(7):980-1000.
6. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006;295(21):2483-91.
7. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037-44.
8. Page BR, Wang EC, White L, et al. Gamma Knife radiosurgery for brain metastases from gastrointestinal primary. J Med Imaging Radiat Oncol. 2017;61(4):522-7.
9. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ. 2001;79(4):373-4.
10. Agboola O, Benoit B, Cross P, et al. Prognostic factors derived from recursive partition analysis (RPA) of Radiation Therapy Oncology Group (RTOG) brain metastases trials applied to surgically resected and irradiated brain metastatic cases. Int J Radiat Oncol Biol Phys. 1998;42(1):155-9.
11. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30(4):419-25.
12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
13. Da Silva AN, Nagayama K, Schlesinger DJ, Sheehan JP. Gamma Knife surgery for brain metastases from gastrointestinal cancer. J Neurosurg. 2009;111(3):423-30.
14. Paudel N, Helenowski I, Kane L, et al. Stereotactic radiosurgery for the treatment of brain metastasis from gastrointestinal primary cancers. J Radiosurg SBRT. 2019;6(1):27-34.
15. Sanghvi SM, Lischalk JW, Cai L, et al. Clinical outcomes of gastrointestinal brain metastases treated with radiotherapy. Radiat Oncol. 2017;12(1):43.
16. Navarria P, Minniti G, Clerici E, et al. Brain metastases from primary colorectal cancer: is radiosurgery an effective treatment approach? Results of a multicenter study of the radiation and clinical oncology Italian association (AIRO). Br J Radiol. 2020;93(1116):20200951.
17. Singh R, Bowden G, Mathieu D, et al. Local control and survival outcomes after stereotactic radiosurgery for brain metastases from gastrointestinal primaries: an international multicenter analysis. Neurosurgery. 2023;93(3):592-8.
18. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2015;91(4):710-7.
19. Yamamoto M, Serizawa T, Sato Y, et al. Stereotactic radiosurgery results for patients with brain metastases from gastrointestinal cancer: a retrospective cohort study of 802 patients with GI-GPA validity test. Adv Radiat Oncol. 2021;6(6):100721.

20. Hasegawa T, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brain metastases from gastrointestinal tract cancer. Surg Neurol. 2003;60(6):506-15.
21. Han JH, Kim DG, Chung HT, et al. Radiosurgery for brain metastasis from advanced gastric cancer. Acta Neurochir (Wien). 2010;152(4):605-10.
22. Park YS, Chang JH, Chang JW, Park YG. The efficacy of gamma knife radiosurgery for advanced gastric cancer with brain metastases. J Neurooncol. 2011;103(3):513-21.
23. Zheng C, Weng Y, Xu Q. Stereotactic radiosurgery for the treatment of esophageal carcinoma brain metastases. J BUON. 2021;26(5):2126-30.
24. Gu XD, Cai YT, Zhou YM, Li ZY, Xiang JB, Chen ZY. Prognostic factors and multidisciplinary treatment modalities for brain metastases from colorectal cancer: analysis of 93 patients. BMC Cancer. 2015;15:902.
25. Li Y, Wu J, Liu F, et al. Single-fraction SRS and multiple-fraction SRT for brain metastases from colorectal cancer. Front Oncol. 2022;12:1060570.