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The coexistence of gastrointestinal stromal tumors and malignancies: Our 10-year results

Yavuz Selim Angın, Cengiz Ceylan, Kutay Sağlam, Cemalettin Aydın

Department of General Surgery, İnönü University Faculty of Medicine, Malatya, Türkiye

ABSTRACT

Objective: Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors in the gastrointestinal system, occurring frequently after epithelial tumors. Although rare, secondary epithelial malignancies can be associated with GISTs. It was planned to conduct a retrospective cohort study evaluating the coexistence of GISTs with malignancies and their long-term outcomes through clinical and pathological findings.

Material and Methods: Demographic and clinicopathological data of 69 patients who underwent surgery for GIST between January 2011 and November 2021 were retrieved from the patient database. Variables between the groups with only GIST and those with a secondary malignancy alongside GIST were analyzed using the Chi-square test and Mann-Whitney U test. Long-term survival analyses were conducted using the Kaplan-Meier test. A p-value of <0.05 was considered statistically significant.

Results: Out of the 69 patients in our population, 40 (58%) were male, and the median age was 65 years (interquartile range= 56-75). GIST was the most commonly located in the stomach (59.4%), and nine (13%) patients had a secondary malignancy. Tumor size, smooth muscle antibody (SMA), and S100 antibody expression showed significant differences between the groups (p< 0.001, p= 0.015, p= 0.006). Shorter survival was observed in patients with GIST plus secondary malignancy (p= 0.005).

Conclusion: The incidence of other intraabdominal malignancies occurring alongside GISTs is more common than have been previously thought. While the presence of a secondary malignancy does not impact the overall survival (OS) in GISTs, it was observed that survival is dependent on the primary malignancy. Patients diagnosed with GISTs require thorough investigation and close monitoring for secondary malignancies.

Keywords: Gastrointestinal stromal tumors, synchron, clinicopathological, prognosis

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) originate from the interstitial Cajal cells (ICC) located in the intramuscular layer. Despite being the most common mesenchymal tumors, GISTs constitute only 1-2% of gastrointestinal system cancers (1). They are predominantly observed in individuals aged between 60-69 years and are rare in those below 40 years old. GISTs can occur anywhere in the gastrointestinal system from the esophagus to the anus. However, they are most frequently found in the stomach (2).

The diagnosis of GIST is established histologically in the presence of tyrosine-protein kinase kit (KIT) or cluster of differentiation 34 (CD34) positivity. If the tumor is negative for KIT, CD34, desmin, smooth muscle actin (SMA), and S-100 protein (S-100), additional tests such as discovered on gastrointestinal stromal tumor staining 1 (DOG1) or mutation analysis of the KIT or platelet-derived growth factor receptor-α (PDGFRA) genes are necessary (3).

GISTs are rare compared to epithelial malignancies in the gastrointestinal system, and the expected survival rate in this group is relatively better (4). Tumor aggressiveness is associated with Ki-67 score, mitotic index, tumor size, and localization (4,5). Additionally, GIST can coexist with epithelial malignancies. While it predominantly accompanies gastrointestinal system malignancies, it can also be observed in conjunction with prostate, breast, hematological malignancies, kidney, and lung cancers (6).

A retrospective cohort study was planned to investigate the clinicopathological differences and long-term (10 years) outcomes of GISTs accompanied by secondary malignancy, compared to GISTs alone.

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Corresponding Author
Yavuz Selim Angın
E-mail: dryavuz05@gmail.com

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MATERIAL and METHODS

Study Design and Patients Selection

Demographic and clinicopathological data, postoperative outcomes, and long-term follow-ups of 69 patients operated for GIST between 2011-2021 at our center were obtained from the patient database. The study was approved by the ethics committee. Approval number is 2023/5189.

Inclusion criteria:

- Operable GIST patients aged 18 and above, regardless of the presence of accompanying epithelial malignancy.

Exclusion criteria:

- Patients with distant metastasis.
- Unresectable and recurrent tumors.

Demographic information (age, sex), clinicopathological data (comorbidities, ASA scores, tumor size and localization, Ki-67 score, mitotic index, cluster of differentiation 117 (another name for the KIT protein) (CD117), CD34, DOG1, SMA, S100 statuses), postoperative complications [Clavien Dindo mild (1-2)/ severe (3-4)], the presence of a second primary malignancy, recurrence (localization), risk of GIST recurrence after surgery [National Institutes of Health (NIH) criteria], and overall survival data were retrieved from the patient database (7,8). All patients operated for GIST underwent preoperative thoraco-abdominal computed tomography (CT), endosonography (EUS), and if necessary, magnetic resonance imaging (MRI) for staging. To monitor patients during the follow-up period, we employed a rigorous imaging schedule, which included CT scans conducted every six months and annual PET scans to ensure any emerging malignancies were detected as early as possible. This protocol allowed for the timely identification of secondary malignancies that were not apparent at the time of the initial GIST diagnosis.

The population was divided into two groups: GIST with accompanying second primary malignancy and GIST alone.

Patient Management

Patients with suspected GIST based on radiological or endoscopic findings and having resectable tumors were operated. Those with accompanying secondary malignancies along with GIST received a pathological diagnosis in the preoperative period. Radical surgery was performed for patients with accompanying secondary malignancies. R0 resection was achieved for GIST cases. Disease staging was performed according to the American Joint Committee on Cancer (AJCC 8) criteria. After surgery, pathology reports were reevaluated, and appropriate patients received adjuvant therapy. All patients were scheduled for outpatient follow-ups every three months for the first two years postoperatively, followed by semiannual appointments for the next three years.

Statistical Analysis

Compliance of numerical data with normal distribution was controlled by Shapiro Wilk test. It was determined that none of the variables showed a normal distribution. Continuous variables were analyzed with the Mann-Whitney U test. Median and interquartile range (IQR) values of these variables were given. Chi-square analysis was performed for categorical variables. Surveillance analysis between groups was done with Kaplan-Meier.

RESULTS

Among the 69 patients who underwent surgery and were followed up due to GIST, median age was 65 years (range= 56-75), with 40 (58%) being male. Patients with more than two comorbidities accounted for 30.4% of the population, with the majority having ASA 1 (4.3%) and ASA 2 (60.9%) operative risk. The most common site of GIST localization was the stomach (59.4%), followed by the jejunum-ileum (21.7%). The presence of accompanying secondary malignancy was observed in nine patients (13%) (Table 1).

In our study, out of the nine patients diagnosed with gastrointestinal stromal tumors with additional malignancies, two malignancies were detected during the follow-up period after the initial GIST diagnosis. These secondary malignancies were identified 12 and 18 months following the GIST diagnosis. At the time of the initial GIST diagnosis, imaging methods, including computed tomography (CT) and positron emission tomography (PET) scans did not reveal the presence of these secondary tumors.

In the analyses conducted between the two groups, there were no statistical differences in terms of age, sex, comorbidity, histological type, mitotic index, and Ki-67 ($p> 0.05$). However, the tumor size in the group with secondary malignancy [3 cm (2-3)] was significantly smaller compared to the group with only GIST [8 (5-16)] ($p< 0.001$).

Following pathological examinations, there were no statistical differences between the groups in terms of CD117, CD34, and DOG1. However, there were statistically significant differences in SMA ($p= 0.015$) and S100 ($p= 0.006$) status (Table 2).

There were no statistically significant differences between the groups in terms of postoperative complications, length of hospital stay [seven days (5-10) vs. 10 days (7-15)], residual tumor classification [R1= 10 (16.7%) vs. 1 (11.1%)], recurrences [12 (20%) vs. 0 (0%)], and mortality [11 (18.3%) vs. 2 (22.2%)]. However, there was a statistically significant difference between the groups in terms of postoperative recurrence risk (NIH classification) ($p= 0.001$). In recurrence risk scoring, 63.3% of the patients in the GIST group were classified as high risk, whereas the majority of the patients in the GIST plus secondary malignancy group (55.6%) were classified as very low risk (Table 3).

Table 1. Demographic data and tumor locations of the population

Variables		Median	Count (%)
Age, year		65 (56-75)	
Sex	Male		40 (58%)
	Female		29 (42%)
Comorbidty	Absent		22 (31.9%)
	1-2		26 (37.7%)
	3≤		21(30.4%)
ASA	1		3 (4.3%)
	2		42 (60.9%)
	3		24 (34.8%)
Tumor localization	Stomach		41 (59.4%)
	Jejunum-ileum		15 (21.7%)
	Duodenum		2 (2.9%)
	Retroperitoneum		0 (0%)
	Colon		4 (5.8%)
	Rectum		0 (0%)
	Intesinal mesentery		5 (7.2%)
	Liver		1 (1.4%)
	Anal canal		1 (1.4%)
GIST plus secondary malignancy	Absent		60 (87%)
	Present		9 (13%)

ASA: American Society of Anesthesiologists, GIST: Gastrointestinal stromal tumor.

In the group of patients with secondary malignancies accompanying GIST, six out of nine patients were male. GIST, mostly originating from gastric localization, was present. Secondary malignancies in these patients included two colon cancers, two rectal cancers, two hepatocellular carcinomas (liver transplants had been performed before the diagnosis of GIST), one stomach cancer (synchronously detected gastric adenocarcinoma), one breast cancer (detected during follow-ups), and one lung cancer (diagnosed during follow-ups due to GIST) (Table 4).

Survey Analysis Results

The average follow-up period for patients was 47.4 months. During the follow-up period, mortality was observed in 13 patients (18.8%), and recurrence occurred in 12 patients (17.4%). Out of these recurrences, 9 (75%) were in the peritoneum, 2 (16.7%) were in the liver, and 1 (8.3%) was a local recurrence. In the group with only GIST, the average overall survival was 59.2 ± 4.98 months, whereas in the group with GIST plus secondary malignancy, it was 28.2 ± 6.08 months (p= 0.005) (Table 5, Figure 1).

DISCUSSION

In our study, consistent with the literature, GISTs (%13) are accompanied by secondary malignancies (mostly gastrointestinal malignancies) in long-term follow-ups. The occurrence of secondary malignancies accompanying GIST ranges from 4.5% to 33% (6,9,10). Moreover, a meta-analysis has revealed that secondary malignancies are predominantly derived from the gastrointestinal and genitourinary systems (9).

Studies supporting the association between epithelial tumors and GIST, as well as hypotheses attempting to explain this association, exist in the literature. Kawanowa and colleagues have reported microscopic GIST in 35% of the patients operated on for gastric adenocarcinoma (11). In an experimental study by Cohen and colleagues, simultaneous development of gastric cancer and leiomyosarcoma has been demonstrated using nitrosoguanidine and acetylsalicylic acid (12). Moreover, other hypotheses have focused on Helicobacter pylori-induced chronic gastritis and atrophic gastric mucosa as secondary factors, as well as the effects of chemotherapy and radiotherapy (13). Maiorana et al. have reported the potential of a single carcinogenic agent to affect two different tissues in the same organ, leading to the formation of different types of cancer (14). However, Ponti et al. have suggested the hereditary nature of a subset of GISTs negative for KIT and PDGFRA activation mutations, potentially contributing to a multineoplastic process (15). Nevertheless, the common factors and reasons for the tumorigenesis of both epithelial and mesenchymal-origin malignancies remain unproven in the present day.

Table 2. Analysis of the clinicopathological data of the groups

Variables		Only GIST		GIST Plus Seconder Malignancy		p
		Median (IQR)	n (%)	Median (IQR)	n (%)	
Age, year		65 (56-75)		68 (57-76)		0.742
Sex	Male		34 (56.7%)		6 (66.7%)	0.571
	Female		26 (43.3%)		3 (33.3%)	
ASA	1		1 (1.7%)		2 (22.3%)	**0.010**
	2		39 (65%)		3 (33.3%)	
	3		20 (33.3%)		4 (44.4%)	
Comorbidity	0		18 (30%)		4 (44.4%)	0.210
	1-2		25 (41.7%)		1 (11.2%)	
	3≤		17 (28.3%)		4 (44.4%)	
Histological type	Spindle-shaped		32 (53.3%)		4 (44.4%)	0.488
	Epithelioid		10 (16.7%)		3 (33.3%)	
	Mix		18 (30.0%)		2 (22.3%)	
Mitotic index		4 (1-14)		1 (1-10)		0.156
Ki-67		5 (2-10)		5 (2-10)		0.879
Tumor size, cm		8 (5-16)		3 (2-3)		**<0.001**
Tumor cut-off	<4		7 (11.7%)		7 (77.8%)	**<0.001**
	≥4		53 (88.3%)		2 (22.2%)	
SMA	Positive		39 (65%)		2 (22.2%)	**0.015**
S100	Positive		6 (10%)		4 (44.4%)	**0.006**
CD117	Positive		53 (88.3%)		8 (88.9%)	0.961
CD34	Positive		41 (69.5%)		9 (100%)	0.053
DOG1	Positive		47 (78.3%)		9 (100%)	0.121

IQR: Interquartile range, ASA: American Society of Anesthesiologists, KIT: Tyrosine-protein kinase kit, CD34: Cluster of differentiation 34, SMA: Smooth muscle actin, S-100: S-100 protein, CD117: Cluster of differentiation 117 (another name for the KIT protein), DOG1: Discovered on GIST-1.

In the literature, the majority of secondary malignancies originate from the gastrointestinal system, particularly the stomach (16-18). Similarly, in our study, six out of the nine tested patients had stomach-originated secondary malignancies. Another noteworthy point is that two of our patients underwent liver transplantation due to hepatocellular cancer. GISTs were incidentally detected during endoscopic examinations due to the close monitoring of these patients. Additionally, non-gastrointestinal cancers were observed in two patients.

In our group of patients with accompanying secondary malignancies, it was observed that the tumor size was statistically significantly smaller, with a low mitotic index, and consequently, a lower risk of tumor recurrence. A similar situation has also been demonstrated in the study conducted by Du et al. We believe that the reason for the smaller tumor size in patients with gastrointestinal system malignancies, either preoperatively synchronously or detected due to another malignancy while under observation, is early detection through the conducted screenings (18).

The most important markers for identifying GISTs are CD117 and CD34. Therefore, the majority of GISTs are positive for CD117 (>95%) and/or CD34 (40%) (19). The simultaneous detection of both CD117 and CD34 is a common feature in most patients. In our case series, there was no significant difference between the group with synchronous malignancy in terms of CD117 and CD34 and the group with only GIST. However, there was a significant difference between the two groups in terms of SMA (p= 0.033) and S100 (p= 0.045). While SMA was proportionally higher in the GIST-only group (65% vs. 22.2%), S100 was higher in the GIST plus secondary malignancy group (10% vs. 44.4%).

Although overall survival was lower in the GIST plus secondary malignancy group, we believe this is not due to GIST itself because of the low recurrence risks. Instead, it is likely that the

Table 3. Surgical and clinical follow-up outcomes of the groups in the postoperative period

		Only GIST		GIST Plus Secondary Malignancy		
Variables		**n (%)**	**Median (IQR)**	**n (%)**	**Median (IQR)**	**p**
Postoperative complication	CD 1-2	26 (44.8%)		1 (11.1%)		0.147
	CD 3-4	10 (17.2%)		3 (33.3%)		
Length of stay hospital, day			7 (5-10)		10 (7-15)	0.294
Resudual tumor classification	R0	50 (83.3%)		8 (88.9%)		0.671
	R1	10 (16.7%)		1 (11.1%)		
	R2	0 (0%)		0 (0%)		
NIH	Very low	4 (6.7%)		5 (55.6%)		**0.001**
	Low	6 (10%)		1 (11.1%)		
	Intermediate	12 (20%)		0 (0%)		
	High	38 (63.3%)		3 (33.3%)		
Postoperative chemotherapy	Absence	29 (48.3%)		3 (33.3%)		**<0.001**
	Imatinib	31 (51.7%)		0 (0%)		
	Adjuvant	0 (0%)		6 (66.7%)		
Recurrence		12 (20%)		0 (0%)		0.140
Recurrence localization	Absence	48 (80%)		9 (100%)		
	Peritoneum	9 (15%)		0 (0%)		
	Liver	2 (3.3%)		0 (0%)		
	Lung	0 (0%)		0 (0%)		
	Local recurrence	1 (1.7%)		0 (0%)		
Mortality		11 (18.3%)		2 (22.2%)		0.781

GIST: Gastrointestinal stromal tumor, CD: Clavien dindo classification, IQR: Interquartile range, NIH: National Institutes of Health.

Table 4. Clinical and pathological data of the patients with secondary malignancies accompanying GIST

No	Sex	Age (y)	Localization	TD (cm)	MI (x/50 hpf)	Localization	Follow-Up (Months)
1	F	57	Duodenum	3	1	Breast cancer (IDC)	DFS (36)
2	M	83	Stomach	3	1	Colon cancer	Death (12)
3	M	77	Stomach	11	10	Colon cancer	DFS (12)
4	M	50	Jejenum-Ileum	4	10	Lung cancer	Death (10)
5	M	57	Stomach	2	2	HCC (liver Tx)	DFS (24)
6	F	62	Stomach	2	1	HCC (liver Tx)	DFS (60)
7	M	69	Stomach	1	1	Gastric adenoca	DFS (24)
8	M	68	Jejenum-Ileum	2	13	Rectum cancer	DFS (15)
9	F	76	Stomach	3	1	Rectum cancer	DFS (24)

TD: Tumor diameter, MI: Mitotic index, IDC: Invasive ductal carcinoma, DFS: Disease free survival, HCC: Hepatocellular carcinoma.

secondary malignancy directly impacted the expected lifespan. Similar findings were observed in the study by Diamantis and colleagues, where there was no statistical difference in terms of expected lifespan between similar groups (p= 0.19) (20).

While our study provides valuable insights into the association between GISTs and secondary malignancies, several limitations should be acknowledged. First, the sample size is relatively small, which may limit the generalizability of our findings.

Table 5. Analysis of the overall survival rates of the groups

	Mean ± SD	95% CI	p
Only GIST	59.2 ± 4.98	49.56-68.91	**0.005**
GIST plus secondary malignancy	28.2 ± 6.08	16.28-40.10	
Overall	55.8 ± 4.59	46.79-64.80	

SD: Standart deviation, CI: Confidence interval, GIST: Gastrointestinal stromal tumor.

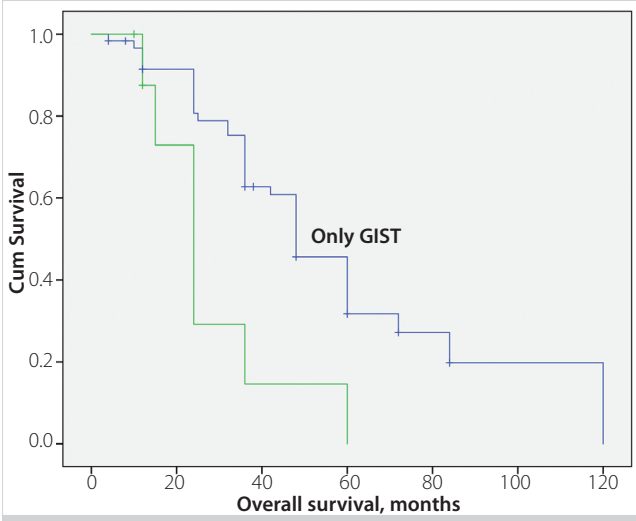

Figure 1. Overall survival rates of patients with only GIST and GIST plus secondary malignancy.

Larger studies with more diverse populations are needed to confirm these results. Second, the retrospective nature of our study may introduce selection bias, third, our study relies on data from a single institution, which may not reflect the broader population. Finally, the lack of longitudinal data limits our ability to assess long-term outcomes and recurrence rates beyond the study period. Future research should aim to address these limitations by including multicenter cohorts and longer follow-up durations.

CONCLUSION

Specifically, we will mention that our sample size is limited and that being a retrospective study may affect the generalizability of the results. Additionally, we recognize that a longer follow-up period and larger sample size would be necessary to fully assess. The frequency of secondary malignancies accompanying GIST is considerable. Furthermore, considering that in such cases the expected lifespan is determined by the presence of secondary malignancy, we recommend preoperative screening for gastrointestinal system malignancies in patients diagnosed with GIST.

Ethics Committee Approval: This study was approved by the İnönü University Scientific Research and Publication Ethics Board Health Sciences Non-Invasive Clinical Research Ethics Board (Decision no: 2023/5189, Date: 14.11.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - CA; Design - YSA; Supervision - CA; Data Collection and/or Processing - KS; Analysis and/or Interpretation - CC; Literature Search - KS; Writing Manuscript - YSA; Critical Reviews - CA.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Gastrointestinal stromal tümörler ve malignitelerin birlikteliği: 10 yıllık sonuçlarımız

Yavuz Selim Angın, Cengiz Ceylan, Kutay Sağlam, Cemalettin Aydın

İnönü Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Malatya, Türkiye

ÖZET

Giriş ve Amaç: Gastrointestinal stromal tümör (GİST) gastrointestinal sistemde en sık görülen mezenkimal tümörlerden biridir ve sıklıkla epitelyal tümörlerden sonra ortaya çıkar. Nadir de olsa, ikincil epitelyal maligniteler GİST'lerle ilişkili olabilir. GİST'lerin malignitelerle birlikteliğini ve uzun dönem sonuçlarını, klinik ve patolojik bulgularla değerlendiren retrospektif bir kohort çalışması planlandı.

Gereç ve Yöntem: Ocak 2011 ve Kasım 2021 tarihleri arasında GİST nedeniyle ameliyat edilen 69 hastanın demografik ve klinikopatolojik verileri hasta veritabanından alındı. Sadece GİST olan ve GİST ile birlikte ikincil malignitesi olan gruplar arasındaki değişkenler ki-kare testi ve Mann-Whitney U testi kullanılarak analiz edildi. Uzun dönem sağkalım analizleri Kaplan-Meier testi kullanılarak yapıldı. p< 0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Popülasyonumuzdaki 69 hastanın 40'ı (%58) erkekti ve ortanca yaş 65 (çeyrekler arası aralık= 56-75) idi. GİST en sık mide yerleşimliydi (%59,4) ve dokuz hastada (%13) ikincil bir malignite vardı. Tümör boyutu, düz kas antikoru (SMA) ve S100 antikor ekspresyonu gruplar arasında anlamlı farklılıklar gösterdi (p< 0,001, p= 0,015, p= 0,006). GİST artı ikincil malignitesi olan hastalarda daha kısa sağkalım gözlendi (p= 0,005).

Sonuç: GİST ile birlikte diğer intraabdominal malignitelerin görülme sıklığı daha önce düşünülenden daha yaygındır. İkincil bir malignitenin varlığı GİST'lerde genel sağkalımı (OS) etkilemezken, sağkalımın birincil maligniteye bağlı olduğu gözlenmiştir. GİST tanısı konan hastaların ikincil maligniteler açısından kapsamlı bir şekilde araştırılması ve yakından izlenmesi gerekmektedir.

Anahtar Kelimeler: Gastrointestinal stromal tümörler, senkron, klinikopatolojik, prognoz

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