RESEARCH ARTICLE

Gastric gastrointestinal stromal tumors. Is there a necessity to use imatinib in the intermediate-risk group?

Yalav O[1], Gumus S[2], Gul MO[2], Eray IC[1], Rencuzogullari A[1]

[1]Department of General Surgery
[2]Department of Surgical Oncology
Faculty of Medicine, Cukurova University, Adana, Turkey

Abstract

Background: A gastrointestinal stromal tumor (GIST) is a tumor that occurs in the gastrointestinal tract, most frequently in the stomach or small intestine. This study aimed to reveal the clinical, histopathological, and immunohistochemical features of patients with GIST and to determine the effect of adjuvant tyrosine kinase inhibitor (TKI) use on survival rates in intermediate-risk gastric GIST cases.

Methods: Clinical characteristics, histopathological findings, and oncological outcomes of 51 patients operated on for gastric GIST between 2010 and 2019 were analyzed retrospectively. Patients treated with neoadjuvant and adjuvant TKI were identified. The effect of adjuvant therapy on survival in the intermediate-risk group was examined.

Results: There were 33 females and 18 males, with a mean age of 64.9 ± 12.8 years. The most common surgical procedure was gastric wedge resection. Three cases were treated with laparoscopy, and 48 underwent open surgery. A multivisceral resection was carried out in three cases. All cases underwent R0 resection. In the intermediate-risk group, there were no statistical differences between individuals receiving adjuvant therapy (n =12) and those not receiving adjuvant therapy (n =6) regarding survival rates (p =0.157). The average follow-up period was 54.9 (min: 2 - max: 106) months. Over this period, in three and five patients, recurrence and metastases occurred, respectively, and seven patients succumbed to the disease. Disease-free survival for five years was 93.7 %, metastasis-free survival was 83.4 %, and overall survival was 86.7 %. HIPPOKRATIA 2021, 25 (3):113-118.

Conclusions: This study showed that adjuvant TKI therapy did not affect survival rates in intermediate-risk gastric GIST.

Keywords: Gastrointestinal stromal tumors, intermediate-risk, adjuvant therapy, imatinib, stomach

Corresponding author: Mehmet Onur Gul, Cukurova University, Faculty of Medicine, Department of Surgical Oncology, Sarıcam, Adana, 01330, Turkey, tel: +905556806729, e-mail: mehmetonurgul@hotmail.com

Introduction

Gastrointestinal stromal tumors (GISTs) constitute 1-2 % of all gastrointestinal neoplasms[1]. GISTs are common in patients over 40 years of age[2]. Before discovering immunohistochemistry and electron microscopy, they were described as leiomyomas, leiomyosarcomas, or leiomyoblastomas due to their sub-epithelial structure. During the last few years, it has been shown that they do not contain smooth muscles or neural structures. The definition of GIST was used for the first time in 1983 by Mazur et al[3]. These tumors originate from interstitial Cajal (ICC) cells called gastrointestinal tract simulator (GI) cells; generally, they contain the tyrosine kinase protein from the KIT receptor[4]. Furthermore, 95 % of these are immunohistochemically positive for KIT (CD117).

The biological behaviors of GISTs are variable. Some were considered benign in the past due to their good histopathological features. However, long-term follow-ups have revealed that although they have useful histopathological features, nearly all GISTs, including those measuring ≤2 cm, may exhibit malignant behaviour[5].

Although GIST can arise in any part of the gastrointestinal (GI) tract, the most common location is the stomach (50-60 %), followed by the small intestine (30-35 %), and colon (5 %)[1-6]. Apart from the digestive system, these can also occur in the omentum, mesentery, peritoneum, and retroperitoneum[7].

The main treatment goal is the surgical removal of the tumor through a negative surgical margin (R0 resection). The tumor size, location, and proximity to adjacent intra-abdominal organs can affect the surgical approach. Treatment may be limited to local resection, or depending on the tumor localization, radical resection or even multiple visceral organ resections may be required[6,7].

This study had two main objectives: i) to reveal the clinical, histopathological, and immunohistochemical features of patients with GIST, and ii) to determine the effect of the use of the adjuvant tyrosine kinase inhibitor (TKI) on survival rates in intermediate-risk gastric GIST cases.

Material and Methods

We retrospectively reviewed data from the hospital database regarding 51 patients who had gastric GIST surgery between 2010 and 2019 in our surgical department. We excluded from the study patients with the coexistence of gastric GIST and gastric adenocarcinomas.

Clinical symptoms, diagnostic methods, tumor characteristics, intraoperative findings, surgical technique, early postoperative results, morbidity, and mortality were analyzed. Tumor localization, size, mitotic index, and immunohistochemical features were identified. Tumors were classified as very low-risk, low-risk, intermediate-risk, or high-risk according to Miettinen's Classification of GIST[7]. We recorded the surgical procedures performed and identified patients receiving neoadjuvant and adjuvant TKI. We divided patients in the intermediate-risk group into two groups, those receiving adjuvant therapy and those not receiving adjuvant therapy, to investigate whether adjuvant therapy affects survival in the intermediate-risk group. The study was approved by the Ethics Committee of Cukurova University, Faculty of Medicine (decision No 95, dated 10/1/2020), and the study protocol conformed to the Declaration of Helsinki's ethical guidelines, as reflected in the institutional committee's prior approval. Written informed consent was taken from every patient who registered for the study.

Statistical Analysis

We performed all statistical analyses using the SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation or median and range values, as presented in the results section. We utilized the Kaplan-Meier test to determine survival rates. We define overall survival as the period from the date of histopathological diagnosis to death from any cause and disease-free survival as the time from the date of primary treatment to recurrence. A p-value lower than 0.05 ($p < 0.05$) was considered statistically significant.

Results

Clinical Findings

Thirty-three females and 18 males had undergone gastric GIST surgery, with a mean age of 64.9 ± 12.8 years. The most frequent complaint was abdominal pain (58.8 %), followed by bleeding (13.7 %), abdominal mass (7.8 %), and chronic anemia (4 %). Eight patients (15.7 %) were clinically asymptomatic and diagnosed incidentally.

Preoperative Evaluation

Except for eight cases diagnosed incidentally, upper GI system endoscopy and abdominal computed tomography (CT) were performed in all patients. Preoperative endoscopic ultrasound (EUS) and fine-needle aspiration biopsy (FNAB) were performed in five cases for whom neoadjuvant treatment was planned.

Operative Findings

The most common surgical procedure performed was gastric wedge resection. Three cases were treated with laparoscopy, and 48 underwent open surgery. Five patients were operated on under emergency conditions, while 46 patients were operated on under optional conditions [perforation (n: 1), gastrointestinal system hemorrhage (n: 2), gastric obstruction (n: 2)]. Multivisceral resection was performed in three cases. Left lateral hepatectomy was performed in one of these cases due to tumor metastasis in liver segment II, whereas transverse colectomy was performed in two cases due to colon invasion (Table 1) (Figure 1). All cases underwent R0 resection.

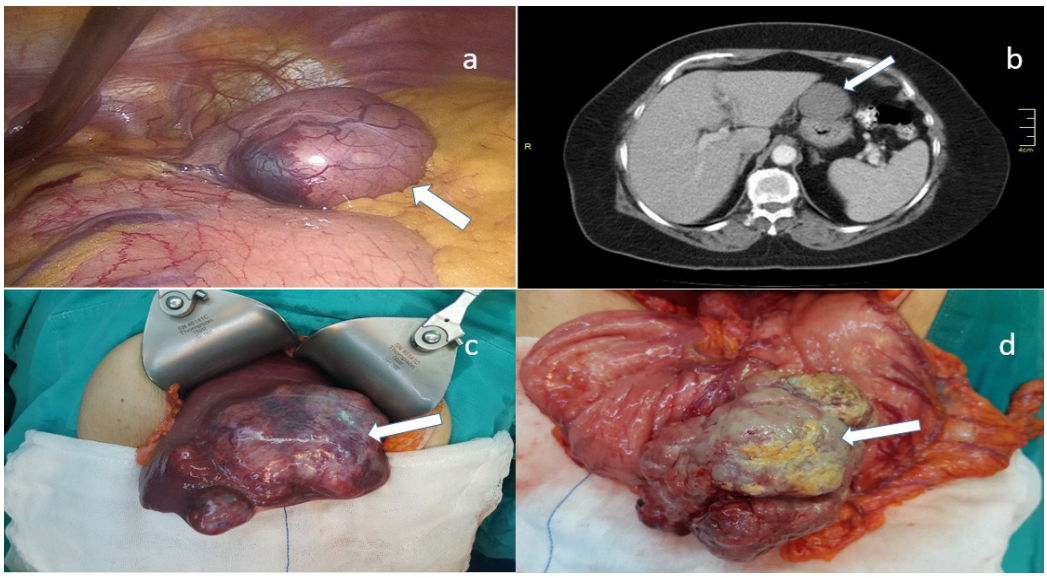

Figure 1: A) Intraoperative image of a gastric stromal tumor (GIST; white arrow) in a patient who underwent laparoscopic wedge resection; B) Computed tomography axial image showing GIST on the anterior wall of the stomach (white arrow); C) Intraoperative image of liver metastasis of the GIST (white arrow); D) Intraoperative image of GIST located in the anterior wall of the gastric antrum.

Table 1: Clinical Features of the 51 patients operated on for gastric stromal tumors included in the current study.

	n: 51	%
Neoadjuvant Therapy		
Yes	5	9.9
No	46	90.1
Surgical Procedures		
Wedge Resection	29	56.9
Proximal Gastrectomy	6	11.7
Subtotal Gastrectomy	9	17.7
Total Gastrectomy	7	13.7
Multivisceral Resection		
Yes	3	5.9
No	48	94.1
Surgical method		
Laparoscopic	3	5.9
Open Surgery	48	94.1

Values are given as number of cases and percentage, n: number.

Pathological Findings

The median tumor size was six (range: 0.3-15) cm. The most frequent tumor stage depending on the size of the primary tumor, was T3. In 11 patients, the tumor invaded the gastric mucosa. The tumor was reported to be exophytic in most cases and had a mitotic index of less than five. The most common type was the spindle cell type. According to Miettinen's risk classification[7], 18 patients were in the intermediate-risk group. Histopathological findings are presented in Table 2.

Table 2: Tumor characteristics and immunohistochemical features of the 51 patients with gastric stromal tumors included in the study.

	(n: 51)	%
Tumor Stage & Size		
T1 (≤2 cm)	3	5.9
T2 (2.1-5 cm)	20	39.2
T3 (5.1-10 cm)	25	49
T4 (>10 cm)	3	5.9
Mucosal Invasion		
Yes	11	21.6
No	40	78.4
Tumor Pattern		
Exophytic	32	62.8
Intramural	6	11.7
Unspecified	13	25.5
Ki67		
Unspecified	3	5.9
Ki67 <10 %	36	70.5
Ki67 >10 %	12	23.6
Risk Classification (AFIP-Miettinen)		
Very Low	3	5.9
Low	14	27.5
Intermediate	18	35.2
High	16	31.4
Mitosis Count /50 HPF		
≤5	33	64.8
>5	18	35.2
Cell Type		
Spindle cell type	36	70.6
Epithelioid type	8	15.7
Mixed type	7	13.7

Values are given as number of cases and percentage, n: number, AFIP: Armed Forces Institute of pathology, HPF: high power fields.

Immunohistochemical Results

Immunohistochemical staining was performed using a cluster of differentiation 117 (CD117), found on GIST-1 (DOG1), smooth muscle actin (SMA), S100, desmin, and CD34 (Figure 2). In cases with negative CD117 and CD34, the diagnosis was provided by DOG1 staining. Positive results were obtained in 38 of 41 patients for DOG1 (focal positive in 0/41 patients), 13 of 47 patients for SMA (focal positive in 20/47 patients), nine of 44 patients for S100 (focal positive in 12/44 patients), one of 45 patients for desmin (focal positive in 1/45 patients), 39 of 46 patients for CD34 (focal positive in 1/46 patients), and 43 of 51 patients for CD117 (focal positive in 3/51 patients).

Postoperative Follow-up

During the postoperative period, adjuvant TKI (400 mg imatinib) was initiated in 27 patients (Table 3). Twelve of these patients were from the intermediate-risk group, and 15 were from the high-risk group.

The average length of follow-up was 54.9 (range: 2-106) months. Over this period, in three and five patients, recurrence and metastases occurred, respectively. One patient who developed recurrence was in the intermediate-risk group, and two were in the high-risk group. Two patients who developed metastasis were in the intermediate-risk group, and three were in the high-risk group. All patients with recurrence or metastasis were in the group that received adjuvant imatinib. Seven patients succumbed to the disease. Disease-free survival for five years was 93.7 %, metastasis-free survival was 83.4 %,

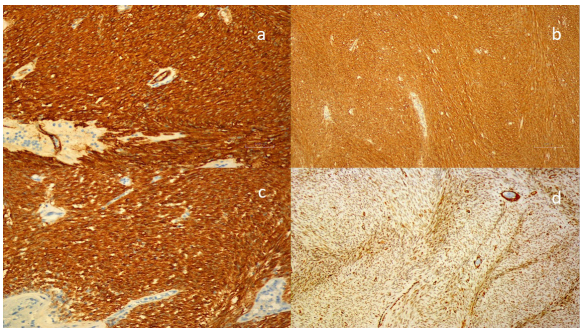

Figure 2: Histopathological findings of gastric stromal tumor (GIST) with A) CD34 histopathological staining (x100), B) CD117 histopathological staining (x100), C) DOG histopathological staining (x100), and D) SMA histopathological staining (x100).

Table 3: Immunotherapy status of the 51 patients with gastric stromal tumors included in the study

	Adjuvant Therapy		
Risk group	**Yes**	**No**	**Total**
Very Low Risk	0	3	3
Low Risk	0	14	14
Intermediate Risk	12	6	18
High Risk	15	1	16
Total	27	24	51

and overall survival was 86.7 % (Figure 3 and Figure 4). The analysis of the patients' results in the intermediate-risk group, divided into two groups, those who received adjuvant therapy and those who did not, showed that adjuvant therapy had no statistically significant effect on survival in the intermediate-risk group (Table 4).

Discussion

In the literature, GISTs have been reported to be most commonly diagnosed in people aged 62 to 75 years[8]. The mean age in the current study was 64.9 ± 12.8 years. In the present study, most patients were women, but the literature is controversial on which gender GISTs are more common[9]. The majority of the patients were women in the present study. Its annual incidence is 3.2-6.8 cases per million in the United States, 2.1-14.5 per million in Europe, and 11.3-19.7 per million in Asia. However, the true incidence is not yet known, and the incidence of gastric GIST lesions identified in autopsy data is significantly higher than expected (22.5 %)[10,11].

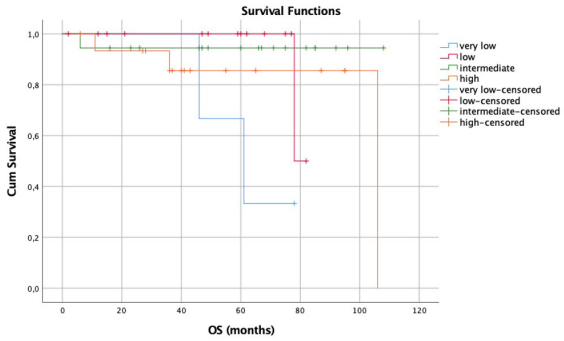

Figure 3: Graph demonstrating the Overall Survival (OS) curve in months of patients with very low-risk, low-risk, intermediate-risk, or high-risk gastric stromal tumor (GIST).

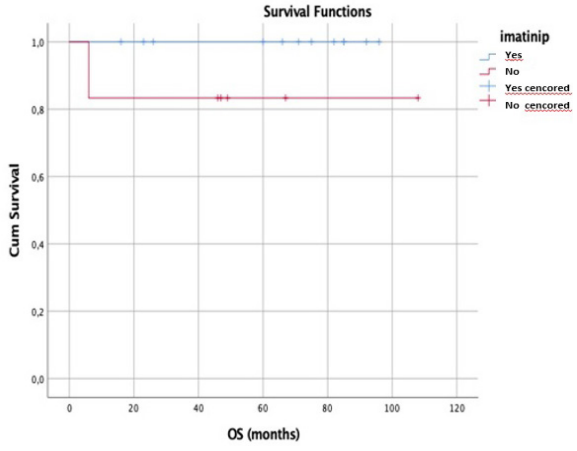

Figure 4: Graph demonstrating the Overall Survival (OS) curve in months of patients with intermediate-risk gastric stromal tumor (GIST) receiving or not adjuvant therapy with Imatinib.

GISTs can develop anywhere in the GI tract, from the esophagus to the anus. Gastric GISTs are more common, and their usual locations are the antrum and corpus of the stomach[12]. It has also been reported that GIST may develop in the omentum, mesentery, and retroperitoneum.

Dematteo reported that GISTs exhibit a wide range of symptoms in their clinical presentation. They are often asymptomatic in the early period as they are usually slow-growing small tumors[13]. Those smaller than two cm are often detected incidentally during endoscopy, radiological examination, or abdominal exploration. Eight of the reported cases were identified incidentally. The most common finding in clinical practice is abdominal pain. Haematemesis, melena, and chronic anemia due to hemorrhagic ulcers caused by erosion of the gastric mucosal tumor are also common findings[14]. The most common finding in the present study was abdominal pain (58.8 %).

Various methods such as GI endoscopy, CT, Magnetic Resonance Imaging (MRI), and upper abdominal ultrasound are utilized in diagnosis. CT with contrast enhancement is valuable for the characterization and evaluation of the lesion, provides information about tumor size and metastasis, and is also used during follow-ups[15]. If a stomach-related lesion is detected on the CT, endoscopic examination is essential to define its relationship with the stomach and a different lesion. Evaluating the internal structure of a submucosal lesion detected by endoscopy and understanding which part of the stomach it originates can only be achieved by EUS. Another advantage of EUS is that it allows biopsy to be taken when necessary to diagnose before surgery[15,16]. In the present study, endoscopic and tomographic examinations were performed in all patients except those identified incidentally.

Endoscopic mucosal biopsies are usually not diagnostic as the tumor is localized in the subepithelial area. Preoperative tissue diagnosis can exclude tumors such as lymphoma, desmoid tumor, carcinoma, or sarcoma in tumors localized outside the stomach[16]. Tissue diagnosis is necessary to establish the definitive diagnosis of GIST for a subepithelial tumor. Preoperative FNAB is not recom-

Table 4: Survival of the intermediate-risk group patients according to their imatinib intake status.

Imatinib Use	EstimateMedian	Std. Error	95 % CI lower bound	95 % CI upper bound	1-year survival	3-year survival	5-year survival	p
Yes	98.9	5.8	96.0	110.4	100.0	100.0	100.0	0.157
No	91.0	15.5	60.5	121.4	83.3	83.3	83.3	

Values regarding survival are given as percentage, CI: Confidence Interval.

mended for surgically resectable masses due to the risk of capsule integrity disruption and implanting tumor cells[16]. In metastatic or high-risk patients, for whom surgery is not primarily considered, FNAB can be performed from the submucosal area under EUS guidance. In this study, invasion into surrounding organs was suspected in five patients, and FNAB under EUS was performed to receive neoadjuvant imatinib therapy. Tumor size was measured at eight to 15 cm in these patients. Proximal gastrectomy was performed in two patients who received neoadjuvant therapy, total gastrectomy in two, and subtotal gastrectomy with colectomy in one.

GISTs localized in the stomach may be intraluminal, intramural, exophytic, pedunculated extramural, or cystic[8,17,18]. In the present study, 62.8 % of gastric GISTs were exophytic.

The pathological diagnosis of GISTs is made based on histological, morphological, and immunohistochemical features[4]. Immunohistochemical staining was positive for CD117, CD34, and SMA in 97 %, 70-80 %, and 20-30 % of GISTs, respectively. Although CD117 is the most common marker, it is not specific to GIST and may be positive in neural, neuroendocrine, or mesenchymal tumours[17-19]. In the present study, CD117 was studied in all patients and was positive in 43 and focally positive in three patients. The diagnosis was confirmed with CD117 in 43/51 patients, and the remaining eight patients were diagnosed with DOG1.

All GISTs are considered to have malignant potential. Miettinen et al[20] categorized malignancy potentials as very low, low, intermediate, and high risk. The most important factors in determining the risk degree are tumor diameter (maximum tumor diameter in cm), mitotic ratio (number of mitosis/50x magnification field), and tumor localization. In the present study, tumor size was larger than five cm in 54.9 % of the cases. The number of mitoses was ≤5 in 64.8 % of the cases, and the Ki67 value was <10 in 70.5 %. In the present study, 5.9 % of the cases were in the very low-risk group, whereas 27.5 % were in low risk, 35.2 % were in medium risk, and 31.4 % were in the high-risk groups.

Surgery is the primary treatment method in resectable GIST cases. In general, wedge resection is sufficient for tumors located in the stomach. Although GISTs can reach large sizes, R0 resection is relatively easy to obtain as they are not very infiltrative. Since lymph node metastases are rare in GISTs, lymph node dissection is rarely required[21-23]. Compatible with the literature, the most common procedure was wedge resection in the present study (56.9 %). In addition to this procedure, a proximal gastrectomy (11.7 %), a subtotal gastrectomy (17.7 %), and a total gastrectomy (13.7 %) were carried out. Malignant GISTs may invade surrounding organs, including the pancreas, transverse colon, or spleen[7]. In the present study, multi-visceral resection was performed in three patients (colectomy in two, left lateral hepatectomy in one).

Recurrence or metastasis is known to develop in about half of the GIST cases undergoing R0 resection within five years[13,24]. In a study by Joensuu et al[24] conducted in 2012, adjuvant treatment with imatinib in high-risk patients was found to prolong both recurrence-free survival and overall survival. In the Z9001 trial, high-risk patients who received adjuvant TKI therapy for one year were compared with the placebo group, and non-recurrence survival was significantly found to be higher in patients receiving adjuvant TKI therapy[13]. These studies have led to the use of TKIs (imatinib mesylate & sunitinib) for the treatment of GISTs patients who are unsuitable for surgical excision, patients whose general condition is not suitable for surgery, cases of recurrent or metastatic GISTs, and patients in the high-risk group. In the SSG XVIII trial, another important randomized-controlled clinical trial was published in the literature, only 400 high-risk patients were evaluated, and it was investigated whether imatinib should be used for 12 months or 36 months[25,26]. Although it was emphasized in this study that better oncology outcomes were achieved using imatinib for 36 months, the results over its usage time are still controversial. However, it needs to be determined in which risk group imatinib should be used. Therefore, each case should be approached individually and evaluated according to anatomical location, tumor size, and mitotic rate. The most substantial issue is whether imatinib will be given as an adjuvant therapy to patients in the intermediate-risk group; this still needs to be clarified[27]. The study that can be a guide in this regard is EORTC-62024[28]. In this study, the results of imatinib use in intermediate-risk and high-risk patients were investigated, and two-year adjuvant therapy with imatinib was concluded not to affect recurrence in the intermediate-risk group. However, GISTs localized in different parts of the GI tract were studied in these trials. Similarly, in a retrospective study by Fu et al[27] involving 85 patients in the intermediate-risk group, imatinib was found not to affect recurrence. However, as in EORTC-62024[28], it was determined that the use of postoperative TKI had no impact on survival in the intermediate-risk group ($p = 0.157$). Only gastric GISTs were studied in the present study, allowing us to evaluate the more homogeneous group results. In our study, survival was higher in patients, using imatinib in the intermediate-risk group. However there was no statistically difference.

The main limitations of the current study were its retrospective design and the fact that the mutational status of the patients could not be specified.

Conclusion

Although there are many studies and publications on GISTs in the literature, these tumors are the type that clinicians and pathologists still find challenging to understand and manage. In recent years, targeted therapies have been developed owing to studies investigating these tumors' molecular and genetic characteristics, initiating a new era in managing this disease. However, it is still needs to be determined which patients will benefit from these treatments. This study demonstrated that adjuvant

TKI therapy has no effect on survival rates in intermediate-risk gastric GIST cases.

Conflict of interest

The authors declare no conflict of interest.

References

1. Grignol VP, Termuhlen PM. Gastrointestinal stromal tumor surgery and adjuvant therapy. Surg Clin North Am. 2011; 91: 1079-1087.
2. Kabukoğlu F. Gastrointestinal Stromal Tumor. Med Bull Sisli Etfal Hosp. 2006; 40: 7-14.
3. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol. 1983; 7: 507-519.
4. Cassier PA, Fumagalli E, Rutkowski P, Schöffski P, Van Glabbeke M, Debiec-Rychter M, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res. 2012; 18: 4458-4464.
5. Rubin BP, Fletcher JA, Fletcher CD. Molecular Insights into the Histogenesis and Pathogenesis of Gastrointestinal Stromal Tumors. Int J Surg Pathol. 2000; 8: 5-10.
6. Costache MF, Filip B, Scripcariu DV, Danilă N, Scripcariu V. Management of Gastric Stromal Tumour - Multicenter Observational Study. Chirurgia (Bucur). 2018; 113: 780-788.
7. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006; 23: 70-83.
8. Mastalier Manolescu BS, Popp CG, Popescu V, Andraş D, Zurac SA, Berceanu C, et al. Novel perspectives on gastrointestinal stromal tumors (GISTs). Rom J Morphol Embryol. 2017; 58: 339-350.
9. Kim IH, Kim IH, Kwak SG, Kim SW, Chae HD. Gastrointestinal stromal tumors (GISTs) of the stomach: a multicenter, retrospective study of curatively resected gastric GISTs. Ann Surg Treat Res. 2014; 87: 298-303.
10. Abraham SC, Krasinskas AM, Hofstetter WL, Swisher SG, Wu TT. "Seedling" mesenchymal tumors (gastrointestinal stromal tumors and leiomyomas) are common incidental tumors of the esophagogastric junction. Am J Surg Pathol. 2007; 31: 1629-1635.
11. Agaimy A, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, Gaumann A, et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol. 2007; 31: 113-120.
12. Laurini JA, Carter JE. Gastrointestinal stromal tumors: a review of the literature. Arch Pathol Lab Med. 2010; 134: 134-141.
13. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373: 1097-1104.
14. Caterino S, Lorenzon L, Petrucciani N, Iannicelli E, Pilozzi E, Romiti A, et al. Gastrointestinal stromal tumors: correlation between symptoms at presentation, tumor location and prognostic factors in 47 consecutive patients. World J Surg Oncol. 2011; 9: 13.
15. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29: iv68-iv78.
16. Dizdar Ö, Güler N. Gastrointestinal stromal tumorler ve imatinib tedavisi. Hacettepe Tıp Dergisi. 2004; 35: 87-91.
17. Corless CL, Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev Pathol. 2008; 3: 557-586.
18. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006; 130: 1466-1478.
19. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol. 2000; 13: 577-585.
20. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005; 29: 52-68.
21. Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, et al. Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol. 2016; 2: 922-928.
22. Miettinen M, Lasota J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs) - a review. Int J Biochem Cell Biol. 2014; 53: 514-519.
23. Dudzisz-Śledź M, Klimczak A, Bylina E, Rutkowski P. Treatment of Gastrointestinal Stromal Tumors (GISTs): A Focus on Younger Patients. Cancers (Basel). 2022; 14: 2831.
24. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012; 307: 1265-1272.
25. Eisenberg BL. The SSG XVIII/AIO trial: results change the current adjuvant treatment recommendations for gastrointestinal stromal tumors. Am J Clin Oncol. 2013; 36: 89-90.
26. Sunamak O, Gul MO, Subasi IE, Donmez T, Ozkara S. Gastrointestinal Stromal Tumours. J Coll Physicians Surg Pak. 2021; 31: 1089-1093.
27. Fu Y, Hao H, Guo L, Yang G, Zhang X. Retrospective analysis of 85 cases of intermediate-risk gastrointestinal stromal tumor. Oncotarget. 2017; 8: 10136-10144.
28. Casali PG, Le Cesne A, Poveda Velasco A, Kotasek D, Rutkowski P, Hohenberger P, et al. Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated with Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol. 2015; 33: 4276-4283.