Clinicopathologic Characteristics and Prognostic Factors of GIST: NCI 5-year Experience

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Introduction: Gastrointestinal stromal tumors (GISTs) are considered the most prevelant mesenchymal tumors in the gastrointestinal system.

Aim of work: This study aims to evaluate the prognostic variables and clinicopathological features in GIST patients treated in the national cancer institute.

Patients and methods: Ninety non-metastatic GISTs treated with curative surgery between January 2016 and December 2020, were the subject of a retrospective investigation. The Cox regression model and the Kaplan-Meier technique were used to evaluate survival analysis.

Results: The mean age was 59.4±13.3 years, 48.9% were males. Tumors were gastric (77.8%), jejunal and ileal (10%) duodenal (6.7%), and rectal (4.4%). Spindle cell tumors constituted 90%. The median mitotic index was 6/50 HPF (1-14), and 49% were > 5. Cases were low-risk (16.7%), intermediate-risk (22.2%), and high-risk (61.1%). Most samples tested positive for CD117 (94.4%) and DOG1 (98.3%). Imatinib was used in 14 patients (15.6%) as neoadjuvant and as adjuvant therapy in 65 (72.2%). The 3-year OS and DFS rates were 92.2% (95% CI: 86.9–99.3) and 70.9% (95% CI: 60.7–82.7), respectively. Rectal tumors showed significantly worse OS (P=0.026). Larger tumor size, non-gastric location, mixed histological subtype, high risk, tumor rupture, and higher mitotic rate were associated with worse DFS. Tumor location was the only independent factor affecting DFS.

Conclusion: GISTs were mostly gastric and intermediate to high risk. Imatinib was more commonly used as adjuvant therapy. Rectal tumors had significantly worse overall survival. Large tumors, non-gastric, mixed histological subtype, high risk, tumor rupture, and higher mitotic rate were associated with worse disease-free survival.

Key words: GIST, gastrointestinal stromal tumors, small intestine, imatinib therapy, KIT.

Introduction

Gastrointestinal stromal tumors (GISTs) are considered the most prevelant mesenchymal tumors in the gastrointestinal system. With no standared method for diagnosis, the incidence rate of GIST is variable. Several studies reported an incidence rate of 10–15 cases per million year. The stomach is the most common site and accounts for about (55.6%) of all GIST Tumors, next comes the small bowel (31.8%), colorectal (6.0%), other/various places (5.5%), and esophageal (0.7%).[1] The interstitial cells of Cajal, which are considered the pacemaker cells that control the intestinal peristalsis, are thought to be the precursors of these tumours. Activation mutation of KIT or PDGFRA oncogene is considered the main pathogenesis of this type of tumors.[2]

Radical surgery is the cornerstone method in treatment of GIST as it cures up to 60% of patients with isolated primary GIST.[3] Nearly half of these patients experienced a recurrence of the illness within five years after surgery, according to DeMatteo et al.[4] A focused molecular treatment for GISTs has emerged in recent years: imatinib, a selective protein tyrosine kinase inhibitor and for now imatinib is considered the main accepted therapy for metastatic or recurrent GISTs.[5,6]

There is extreme variability in the biological behaviour of GISTs, and the risk indicators are not always clear.[7] The best risk classification system for GISTs is still unknown, despite the fact that several have been presented.[8] The most often used classification in clinical practice is the updated National Institutes of Health (NIH) classification, which combines the advantages of the Armed Forces Institute of Pathology (AFIP) and NIH criteria, especially when the rupture happens before to or during surgery.[9] Furthermore, Ki67 expression has been linked in a number of studies to the prognosis of postoperative GISTs.[7,10,11]

It was once believed that malignant GISTs were very resistant to treatment, and that few patients showed appreciable clinical improvement following standard chemotherapy and/or radiation therapy. Furthermore, mesenchymal tumours were not well acknowledged as distinct entities prior to the development of appropriate diagnostic techniques.[12,13]

Morphological evaluation, positive CD117 and DOG1 immunohistochemistry findings, and KIT and PDGFRA gene mutation studies are all necessary for the diagnosis of GISTs.[14-16] Although more asymptomatic GISTs are being diagnosed at an early stage due to the increased use of abdominal computed tomography (CT), magnetic resonance imaging (MRI), and endoscopy, it is still unclear how early detection affects prognosis.[17]

The behavior of GISTs differs from accidental small asymptomatic tumors to those exhibiting significant metastasis. Tumour size, mitotic activity, and anatomical location all influence the probability of malignant behaviour.[18-22] With the introduction

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of the tyrosine kinase inhibitor (TKI) imatinib mesylate in 2002, the survival rates of GISTs rose dramatically.[23-25]

There aren't many researches on the clinicopathological features of GIST in Egypt. Examining the clinicopathological and immunophenotypic features of GISTs at the National Cancer Institute in Egypt as well as looking into their prognostic variables are the goals of this retrospective study.

Patients and methods

Ninety patients who had gastrointestinal stromal tumours (GISTs) removed from any location through the gastrointestinal tract (GIT) within five years, from January 2016 to December 2020, were included in this retrospective cohort analysis. The research excluded individuals with metastatic disease and those who had incomplete GIST excision.

The patients' age, sex, surgery information, pathology, and follow-up data were gathered. All preoperative investigations including endoscopic tests, such as gastroscopy or colonoscopy or even small bowel capsule endoscopy, and radiological tests as abdominal CT, MRI, and positron emission tomography (PET)-CT, were all recorded. History of imatinib as a surgical adjuvant and preoperative neoadjuvant. The date of surgery, the neoplasm's location, the surgical technique used, any problems after the procedure, and the postoperative mortality prior to discharge are all included in the surgical data. The histopathological information included the tumor's origin, the neoplasm's size, the resection margins, and histological characteristics such penetration into the surrounding tissue or perineural or lymphovascular invasion.

Statistical method

SPSS version 28 was used for data management and statistical analysis (IBM, Armonk, New York, United States). The Shapiro-Wilk test and direct data visualisation techniques were used to evaluate the normality of quantitative data. Means and standard deviations or medians and ranges were used to summarise quantitative data based on normalcy. Numbers and percentages were used to summarise categorical data.

Both the Chi-square and Fisher's exact tests were used to compare the categorical data based on mortality. Both overall and disease-free survival were estimated using Kaplan-Meier analysis. Using the log-rank test, survival was compared based on several characteristics. To forecast survival, a multivariate Cox regression analysis was used. 95% confidence intervals for the hazard ratios were computed. There were two sides to every statistical test. A P-value of less than 0.05 was deemed significant.

Results

In the current investigation, 90 GIST patients were examined. The mean age of patients in this study was 59.4±13.3 years. With 48.9% men and 51.1% females.

The most frequent site of tumours was the stomach (77.8%), followed by the jejunum, and the ileum (10%) and the duodenum (6.7%). Tumour sizes ranged from 3 to 25 cm, with a median of 10 cm. Tumour rupture occurred in 15.6% of the subjects. 90% of histological subtypes were spindle cell tumours, 6.7% were epithelioid cell subtypes, and 3.3% were mixed. Between 1 to 14, the median mitotic index was 6. Furthermore, the Ki-67 proliferation score ranged from 2% to 70%, with a median of 7%. The distribution of risk groups was low-risk 15 (16.7%), intermediate-risk 20 (22.2%), and high-risk 55 (61.1%) based on the NIH criteria **(Table 1).** The lymph nodes of just three individuals were positive.

The main site had a substantial impact on the tumours' mitotic rate (P=0.020). The median mitotic index of rectal tumours was greater than that of stomach tumours (P=0.019). Additionally, it was shown that the mitotic rate was greater in bigger GISTs (R=0.368, p<0.001).

Not all patient's immunohistochemistry findings were available. The majority of GIST samples had positive results for DOG1 (98.3%) and CD117 (94.4%). Furthermore, 91.1% of the samples tested positive for CD34, whereas 37.5% and 20% of the samples showed smooth muscle actin (SMA) and S-100 protein expression, respectively **(Table 2).**

Treatment

Many surgical techniques were carried out, with gasterectomy either partial or total was the most common surgery done (68 patient; 75.6%), small intestinal resection and reanastomosis (12 patients; 13.3%) as local excision (6 patients; 6.7%), lower anterior resection (2 patients; 2.2%), abdominal-perineal resection and Whipple (1 patient; 1.1% for each). The location, size, and likelihood of total excision of the tumour all influenced the surgical method selection.

Fourteen patients (15.6%) with high-risk GISTs (n=13) and intermediate-risk GISTs (n=1) received imatinib as neoadjuvant treatment. While 65 patients (72.2%) did not receive neoadjuvant imatinib treatment and these 65 patients received imatinib as adjuvant treatment. Twenty (22.2%) of the patients experienced postoperative problems.

Survival analysis

The follow-up period ranged from 1 to 123 months, with a median of 35 months. Seven patients passed away, seven experienced a local recurrence, and eleven experienced metastases by the end of the follow-up period. 92.2% (95% CI: 86.9–99.3) and 70.9% (95% CI: 60.7–82.7) were the 3-year OS and DFS rates, respectively. Tables 3 and 4 display the findings of the univariate analysis of possible prognostic variables. Significantly lower OS is linked to rectum tumours (P=0.026). The OS was poorer for intermediate-risk tumours, however the difference was not statistically significant (P=0.068). Otherwise, tumour size, histological subtype, tumour rupture, mitotic index, and neoadjuvant imatinib need had no effect on OS **(Table 3). (Table 4)** shows that lower DFS was linked to larger tumour size (>10 cm), non-gastric disease site, mixed histological subtype, high risk, tumour rupture, greater mitotic rate (>5/50 HPF), and requirement for neoadjuvant imatinib. Tumor site was the sole independent factor influencing DFS, according to the multivariate Cox regression model, with rectal tumors vs gastric tumors showed hazard ratio 6. 44 and (2.06-20.15 CI respectively) and P value was 0.001 indicating high significance of site on DFS.

Table 1: Clinicopathological characteristics of the studied group

	Value
Tumor Location	
Stomach	70 (77.8%)
Duodenum	6 (6.7%)
Ileum	5 (5.6%)
Jejunum	4 (4.4%)
Rectum	3 (3.3%)
Duodenojejunal	1 (1.1%)
Rectosigmoid	1 (1.1%)
Tumor Size (cm)	10 (3-25)
Mitotic index (/50 HPF)	6 (1-14)
Ki67 (%), n=13	7 (2-70)
Tumor rupture	14 (15.6%)
Histological subtype	
Epithelioid cell	6 (6.7%)
Spindle and epithelioid cells	3 (3.3%)
Spindle cell	81 (90%)
Risk Stratification	
High risk	55 (61.1%)
Intermediate risk	20 (22.2%)
Low risk	15 (16.7%)

Table 2: Immunohistochemistry findings of the studied group

	n	Positive N (%)
CD117	90	85 (94.4%)
DOG-1	58	57 (98.3%)
CD34	45	41 (91.1%)
S100	35	7 (20%)
SMA	16	6 (37.5)

Table 3: Overall survival in the studied group and the prognostic factors

	n	Events	Cumulative survival (%) at 36 months	P-value
Whole group	90	7	92.9	
Size				
≤ 10 cm	43	4	90.7	0.734
> 10 cm	47	3	85.2	
Location				
Stomach	70	4	94.6	
Small Intestine	16	1	91.7	0.026
Rectal	4	2	75.0	
Tumor Histology				
Spindle	81	6	93.3	
Epithelioid	6	1	83.3	0.411
Mixed	3	0	100.0	
Risk				
Low	15	0	100.0	
Intermediate	20	4	88.2	0.068
High	55	3	92.9	
Rupture				
Yes	14	2	91.7	0.581
No	76	5	93.1	
Mitotic Index				
≤ 5/5 HPF	46	4	92.2	0.670
> 5/5 HPF	44	3	93.7	
Neoadjuvant Imatinib				
Yes	14	0	100.0	0.122
No	76	7	91.3	
Adjuvant Imatinib				
Yes	65	6	92.0	0.550
No	25	1	96.0	

Table 4: Disease-free survival in the studied group and the prognostic factors

	n	Events	Cumulative survival (%) at 36 months	P-value
Whole group	90	23	70.9	
Size				
≤ 10 cm	43	17	57.6	0.010
> 10 cm	47	6	85.7	
Location				
Stomach	70	14	78.6	
Small Intestine	16	5	59.5	0.001
Rectal	4	4	0.0	
Tumor Histology				
Spindle	81	19	72.9	
Epithelioid	6	2	66.7	0.039
Mixed	3	2	33.3	
Risk				
Low	15	0	100.0	
Intermediate	20	4	81.3	0.017
High	55	19	60.4	
Rupture				
Yes	14	7	49.0	0.036
No	76	16	75.7	
Mitotic Index				
≤ 5/5 HPF	46	17	57.6	0.010
> 5/5 HPF	44	6	85.7	
Neoadjuvant Imatinib				
Yes	14	7	38.4	0.006
No	76	16	76.6	
Adjuvant Imatinib				
Yes	65	21	64.4	0.025
No	25	2	88.6	

Discussion

This retrospective investigation evaluated the clinicopathologic characteristics and prognostic outcomes of patients treated for gastrointestinal stromal tumours (GISTs) at Cairo University's National Cancer Institute. The findings align with previous studies conducted on other demographics. The average age of the patients in this study was roughly 60. stomach. The tumor's location was the sole independent factor affecting DFS.

GISTs are most commonly found in people between the ages of 50 and 70, while they can occur at any age. The patients in this study were 59.4±13.3 years old on average. This is in line with the age at diagnosis, per a number of previous studies.[26-28]

This study demostrated that stomach has the highest percentage of GISTs in our sample (77.8%), followed by the small intestine. Which comes in line with international research, indicating that stomach accounts for 60-70% of cases and the small intestine for 20-30% of cases.[29] A Chinese study reported a comparable incidence of stomach GISTs of 73.1%.[30] However, other studies revealed that stomach tumours were less frequent. Khan et al.[26] found a lower prevalence of gastric tumours (57%), but Sakin et al.[28] reported 51.4% of stomach tumours. Similarly, Li et al.[31] discovered that the stomach was the most often discovered tumour location (49.1%) in their study of Chinese patients.

In the current study, 61.1% of patients were classified as high risk, 22.2% as intermediate risk, and 16.7% as low risk. The percentage of those with positive lymph nodes was just 3.3%. In a busy university hospital, high-risk tumours were present in 50.4% of GIST patients.[32] Furthermore, the percentage of patients with positive LN findings was just 1.5%. Prior studies indicated between 30 and 40 percent of high-risk individuals.[27,28]

GISTs are divided into four groups according to

the National Institutes of Health's (NIH) criteria, which take into account the tumor's size, location, number of mitoses, and rupture.[9] In general, GISTs classified as intermediate or high risk are thought to be malignant, whereas those classed as very low or low risk are thought to be possibly malignant. Different therapeutic approaches for the same GIST lesion derive from individual differences in malignant potential.[33] The reported proliferation index ranged from 2% to 70%, with a value of 7%. Non-gastric tumours made up 22.2% of the patients in this investigation. 52.2% of the cases were tumours larger than 10 cm in diameter. Between 1 and 14, the median mitotic index was 6/50 HPF. Of the patients, 49% had a mitotic index more than 5/50 HPF. In addition, a range of 2% to 70% was found for the median Ki-67 proliferation index, which was 7%.

Depending on the size and location of the tumour, each patient had a different surgical technique with the goal of curing their condition. A small percentage of patients, primarily those with big or anatomically problematic tumours, received neoadjuvant imatinib. As a specific inhibitor of KIT, imatinib seeks to decrease tumour size, make surgical resection easier, lower the chance of recurrence, and enhance overall results. In the current research, DFS was 38.4% for patients treated with neoadjuvant imatinib and 76.6% for those not receiving neoadjuvant treatment (P=0.006).

Imatinib has had a major influence on outcome improvements, especially in high-risk patients, according to the research. In a pooled study of 161 patients with locally advanced GISTs, neoadjuvant imatinib achieved exceptional long-term results. Only two patients experienced disease progression, and 83% of cases had tumour excision that was R0. The disease-specific survival rate at 5 years was 65%.[34] The Radiation Therapy Oncology Group (RTOG) carried out a multicenter study to assess the efficacy of adjuvant and neoadjuvant imatinib in GISTs. In the neoadjuvant group, imatinib was given to patients with large or moderately resectable GISTs for 8-12 weeks before surgery. The study demonstrated a 67% radiologic response rate, significant tumour size reductions, and improved surgical outcomes.[35] A worldwide phase II study looked at neoadjuvant imatinib therapy for individuals with gastric GISTs ≥10 cm. The R0 resection rate was 91%, and 88% of patients were able to save at least half of their stomach.[36]

In contrast, 72% of the patients in the current trial received imatinib as an adjuvant treatment. The tumours in each of these individuals were moderate or high risk. Adjuvant imatinib did not affect OS (P=0.550), however it was linked to a superior DFS of 88.6% as opposed to 64.4% in those who did not get adjuvant treatment (P=0.025). This result is in line with a number of other studies in the literature that shown adjuvant imatinib treatment improved patients' recurrence-free survival.[37-39] Randomised studies, however, did not demonstrate a beneficial effect on overall survival.[37,40] Consequently, 3-year adjuvant imatinib therapy is recommended by established treatment recommendations for GIST patients with a high estimated risk of recurrence.[41]

Imatinib blocks downstream signalling pathways linked to angiogenesis, cell proliferation, and survival by competitively blocking the ATP-binding site of the KIT and PDGFRA receptors.[42] In the current investigation, 94.4% of the patients have C-KIT (CD117). In this investigation, other immunohistochemistry markers were also found. Unfortunately, not every patient had access to immunohistochemistry data. Of the samples that were available, 98.3% had DOG1, 91.1% contained CD34, 37.5% contained SMA, and 20% contained S-100 protein.

These results are similar to those found in previous research. For instance, in a sample of Chinese patients, 98.4% had positive C Kit expression, 98.3% had positive DOG-1, 94.5% had positive CD34, 57.5% had positive SMA, and 14.2% had positive S-100.[30] Similar results were seen in other investigations.[28,43]

92.2% (95% CI: 86.9–99.3) and 70.9% (95% CI: 60.7–82.7) were the 3-year OS and DFS rates in this study, respectively. Rectal cancers were associated with a lower overall survival rate (75%) compared to stomach and intestinal tumours (P=0.026). Every rectal tumour received adjuvant imatinib. Rectal GIST may be more difficult to remove curatively due to anatomical characteristics such the deep, small pelvis and its close closeness to the sphincter muscle or other organs, which might result in a lower overall survival rate.[44] By the conclusion of the follow-up period, all rectal patients had either local recurrence or distant metastases.

There were no definitive results for OS from risk stratification (P=0.068). Tumour rupture, histological subtype, tumour size, and mitotic index did not affect OS. For patients with localised illnesses who have had curative surgical resection, DFS is a crucial goal in the management of GISTs. Even with successful resection, recurrence rates can be substantial, especially in people with high-risk traits. On univariate analysis, the current study found that poorer DFS was linked to high-risk tumours, tumour size >10 cm, non-gastric disease site, mixed histological subtype, tumour rupture, and mitotic rate >5/50 HPF. The only independent predictor influencing DFS, according to multivariate analysis, was tumour site.

Since it has been demonstrated that tumours larger than 5 cm in diameter with a mitotic count greater

than 5 per 50 HPF, as well as tumours larger than 10 cm regardless of mitotic rate, have a higher risk of recurrence, adjuvant pharmacotherapy is necessary.[19] For tumours of the same size and mitotic count, non-gastric GISTs were more likely to experience a tumour recurrence than gastric GISTs.[45] Previous studies have connected recurrence in GISTs to tumour size, mitotic rate, and tumour location.[27,46]

Notwithstanding its significant discoveries, the study had a number of drawbacks. Its retrospective design could have resulted in selection bias, and the results' generalisability is constrained by the limited sample size. Our ability to connect genetic profiles with treatment responses was further limited by the lack of routine execution of precise molecular testing (e.g., KIT and PDGFRA mutant subtyping) due to budget limitations.

However, this study provides important information about the clinicopathologic range and treatment results of GISTs in a community in Egypt. Expanding access to molecular diagnostics, improving treatment approaches, and putting in place customised surveillance procedures based on proven risk stratification instruments will require ongoing work.

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