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MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS IN GASTROENTEROLOGY AND HEPATOLOGY TEACHING HOSPITAL AND BAGHDAD TEACHING HOSPITAL

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) are tumors believed to originate from the mesenchymal cells of the gastrointestinal tract. And the most common mesenchymal tumor located in the gastrointestinal (GI) tract. In very rare found extra (GI). Gastrointestinal stromal tumors were originally Surgical resection has always been a main treatment because of GISTs resistance to traditional chemotherapy and radiation. **Aim of study:** To reach better assessment and management of the gastrointestinal stromal tumors, with better cure rate for the patients. **Methods:** Between February 2022 and February 2024, 28 consecutive patients (11) women and (17) men with an age (range from 28 to 73 years) were operated on for GIST in the Department of Gastrointestinal surgery in Gastroenterology and hepatology teaching hospital and Baghdad teaching hospital medical city in Baghdad. **Result:** The study consists of 28 patients, male 17 (60.7%) female 11 (39.3) the age range from (28_73) years old (53.6%) more than 60 years old patients. Higher Mitotic index was also tied with larger tumors and also statistical significant ($p<0.001$). Tumor location most commonly found in stomach 18 cases (64.3%) followed by small bowel 5 cases (17.9%). There is statistically significant correlation between age and mitotic index ($p=0.02$). Higher mitotic index was correlated with younger age of the patients. **Conclusion:** To assess proper approach to GIST we must have MDT, to reach obtimal cure of the patients. There is strong correlation between patient age and tumor size with high mitotic index which reveal high malignancy ($p=0.02$ and $p<0.001$, respectively).

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are tumors believed to originate from the mesenchymal cells of the gastrointestinal tract.[1] And the most common mesenchymal tumor located in the gastrointestinal (GI) tract.[2] Most studies have reported the incidence of clinically relevant GISTs at 10-15 per million populations per year. GISTs are found most often in the stomach (56%), small bowel (32%), colon and rectum (6%), esophagus (0.7%), and other locations (5.5%).[3,4] In very rare circumstances, GISTs appear outside of the gastrointestinal tract – they are called extragastrointestinal stromal tumors (eGIST).[5] GISTs occurring outside of the stomach are associated with a higher malignant potential.[6] In 1998 it was found that these tumors actually arise from the interstitial cells of Cajal or similar cells.[7] Most GISTs (>95%) stain positively for CD117 (c-KIT) protein.[8] Around 80% carry a mutation in the c-KIT gene or platelet-derived growth factor receptor-alpha (PDGFRA) gene, which code receptor tyrosine kinase mutations that can be targeted by small molecule pharmacological inhibitors.[2] The diagnosis of GIST can be confirmed by mutational analysis to identify known mutations in the PDGFRA and KIT genes, particularly in rare cases that are CD117-negative and DOG1 negative.[9] Mutational analysis has prognostic value and can predict sensitivity to molecular-targeted therapy[9] For these reasons, current guidelines recommend the inclusion of mutational analysis as standard diagnostic practice for GIST cases.[9] GISTs are usually graded as benign, of uncertain malignant potential, and as malignant.[10] More aggressive GISTs may metastasize to different organs or tissues. They very rarely metastasize to lymph nodes.[11] It is worth noting that the American Joint Cancer Committee/Union for International Cancer Control (AJCC/UICC) grades GISTs separately from other sarcomas, using a two-grade system based on mitotic rate: of low grade (5 mitoses per 5 mm2 or per 50 high-power field (HPF)) and high grade (>5 mitoses per 5 mm2 or per 50

HPF).[12] Current European Society for Medical Oncology (ESMO) guidelines suggest that the standard approach to patients with esophagogastric or duodenal nodules <2 cm is an endoscopic ultrasound assessment and then follow-up, reserving excision for patients whose tumor increases in size or becomes symptomatic.[9] The NCCN guidelines for GISTs recommend that prior to treatment, evaluation and management by a multidisciplinary sarcoma team is performed, including an abdominal/pelvic CT scan with contrast, with or without MRI. Very small gastric GISTs of <2 cm in diameter may be evaluated with endoscopic ultrasound-guided fine-needle aspiration. For GISTs of 2 cm or larger, endoscopy with or without ultrasound may also be indicated.[12] Surgical resection has always been a main treatment because of GISTs resistance to traditional chemotherapy and radiation.[9,13,15] Imatinib has been proven, however, as a very useful drug in selected neoadjuvant settings.[9] It inhibits both c-kit tyrosine kinase mutations and PDGFRA mutations other than D842V.[16] Genetic testing for specific KIT and PDGFRA mutations can predict the patient's response to imatinib and the possible benefit of a higher imatinib dose. In case of imatinib resistance, sunitinib may be considered as a viable option.[9,17] Some GISTs express or gain resistance to both drugs.[9] In recent years, regorafenib was introduced as a third-line treatment.[9,18-19] Conflicting reports about the different clinical and histopathological factors affecting prognosis in patients with GIST have emerged. Therefore, this retrospective study between February 2022 and February 2024 from a duoble centres in Gastroenterology and hepatology teaching hospital and Baghdad teaching hospitals aimed to investigate postoperative outcomes and selected prognostic factors in 28 patients diagnosed with gastrointestinal stromal tumor (GIST) of the stomach, small bowel and large bowel.

PATIENTS AND METHODS

Patients' Characteristics

Between February 2022 and February 2024, 28 consecutive patients (11) women and (17) men with an age (range from 28 to 73 years) were operated on for GIST in the Department of Gastrointestinal surgery in Gastroenterology and hepatology teaching hospital and Baghdad teaching hospital in Baghdad.

Diagnosis of GIST

Patients were diagnosed, treated, and monitored after the surgery according to current ESMO guidelines.[9] Showing in figure 1

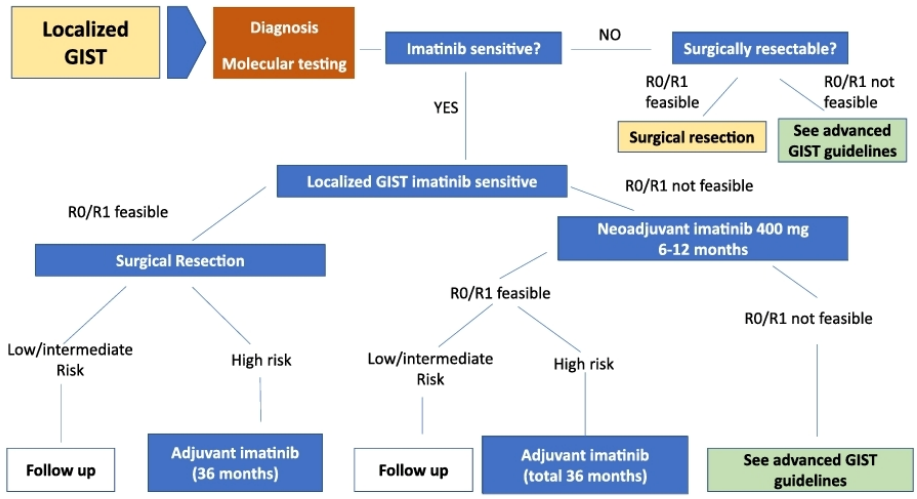

Fig. 1 Algorithm for the management of localized disease

Multidisciplinary treatment planning was conducted, involving participation of a surgeon, gastroenterologist, radiologist, and oncologist. Prior to surgical treatment, radiological and endoscopic examinations (ultrasonography of the abdominal cavity, computed tomography and endoscopic investigations of the upper and lower gastrointestinal tract with tumor biopsy) were performed to check staging of the tumors in TNM classification according to the American Joint Committee on Cancer (AJCC) Staging Manual (7th and 8th edition).[26] If necessary, positron emission tomography (PET) was also conducted. Immunohistochemical investigations of CD117, CD34 and smooth muscle actin (SMA) were carried out to differentiate between GISTs and other mesenchymal neoplasms. They were completed in the Department of Pathology, Medical city of Baghdad, Iraq. About gen mutation in c-kit gen or PDGFRA gen unfortunately not available. Moreover, each patient with confirmed GIST in the above-mentioned examinations was consulted by an anesthesiologist to assess general health and risk of surgery, and to qualify for general anesthesia (taking into account all comorbities).

Management of GIST

Patients with a locally advanced, resectable tumor (without distant metastases) with an acceptable perioperative risk were qualified for elective surgery, we didn't use neoadjuvant because we don't had mass mor than 10 cm.[14] In case of tumor hemorrhage or intestinal obstruction, patients were qualified for urgent surgery due to vital indications. Some tumors were found associated with jundice in duodenum GIST. The aim of the surgical treatment was to obtain R0 resection (macroscopic and microscopic margins without tumor). The type of surgery depended on the location and diameter of the tumor. Based on the intraoperative and postoperative investigations, the tumor size and mitotic index were determined in each patient. GISTs were divided into two groups according to location within the gastrointestinal tract: (1) related to stomach, (2) non-stomach which includes eosophagus duodenum, jejunum, ileum, colon and rectum. In stomach, which is the most common we perform Non-anatomic wedge resection in form of stapled or disk resection which is sometimes needed in near gastroesophageal junction or pylorus to avoid inflow or outflow obstruction or near neural supply of stomach to avoid gastric atonia or partial gastrectomy as shown in figure 2. And GIST tumor in stomach figure 3.

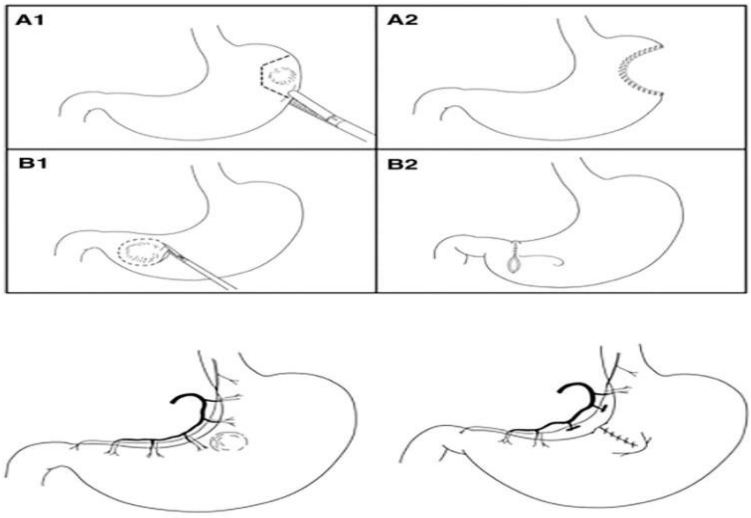

Figure 2: Wedge resection stomach.

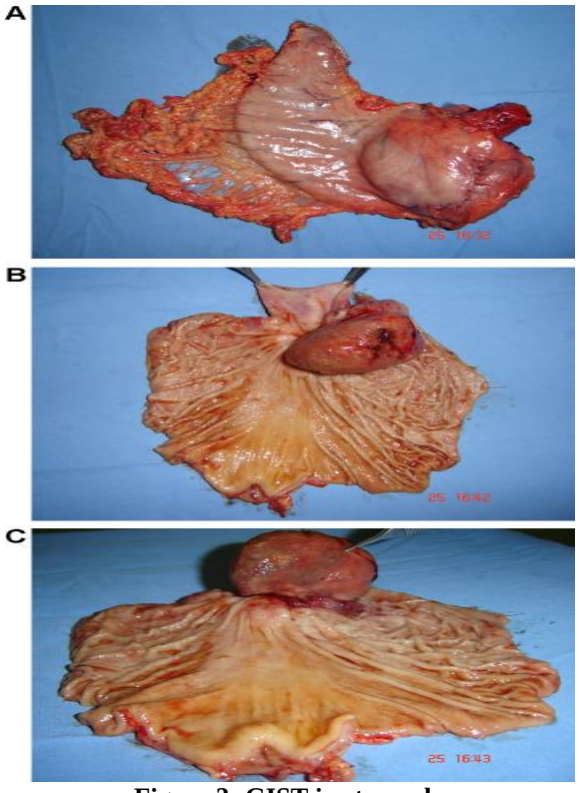

Figure 3: GIST in stomach.

In small and large bowel resection with anastomosis, as shown in figure 4.

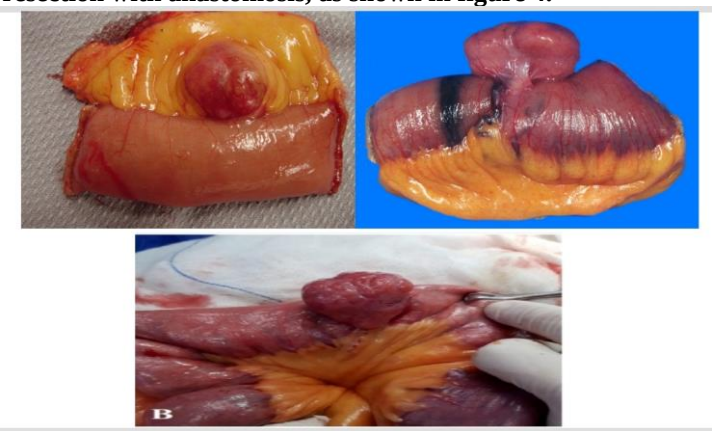

Figure 4: Multiple small bowel GIST toumors.

Whipple procedure performed in duodenal GIST. The tumor size cut-off point was decided to be 5 cm.[11] The mitotic index (MI), defined as the number of mitotic figures in 50 highpower fields (HPF), was assessed. We decided to divide it into 3 groups: A (0-3 cm), B (3-5 cm) (³10) C (>5 cm). The patients were split into 2 age groups (60 years old or >60 years old). The duration of postoperative hospitalization ranged from 5 to 14 days (mean 7 days).

Follow-up

Follow-up of patients was conducted by regular hospital visits and then at 3, 6, and 12 months, and yearly thereafter. Each assignment consisted of a physical examination, and selected imaging procedures were carried out (ultrasound, endoscopy, computed tomography, and laboratory investigations) based on the location, diameter, mitotic index, and the type of resection (R0/ R1). In the case of GIST with high risk of recurrence high mitotic index, rectal location, or applied adjuvant imunetherapy (imatinib), additional chest X-ray every year was conducted. Three patients are lost to follow-up and were excluded from several analyses.

Statistical analysis Detailed descriptive analysis was performed. Correlation between sex, age, tumor location, mitotic index, tumor size, imatinib treatment and survival of patients was assessed. Results were subjected to statistical analysis, where $p<0.05$ was considered to be significant. This study takes into account tumor size, mitotic count, tumor site, and rupture. It is also worth noting that the data are solely comprised of patients that were treated via surgery alone. All calculations and statistical analysis were performed in IBM SPSS Statistics 23.

RESULTS

Patient characteristics

The study consists of 28 patients, male 17 (60.7%) female 11 (39.3 %) the age range from (28_73) years old (53.6%) more than 60 years old patients, Table 1.

Table 1

pt. age * pt. sex Crosstabulation

Count

		pt. sex		Total
		male	female	
pt. age	21_30	0	1	1
	31_40	4	3	7
	41_50	2	0	2
	51_60	3	0	3
	more than 60	8	7	15
Total		17	11	28

Surgical treatment

There were numerous surgical procedures used in the study, Surgical approach depended on tumor location, size, and the prospect of complete resection. A wedge gastric excision was the most frequent surgical procedure 13 cases (46.4%) followed by stomach resection in form of distal, proximal and subtotal gastrectomy 5 cases (17.9%) and others as shown in table 2.

Table 2

type of surgery

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	stomach wedge resection	13	46.4	46.4	46.4
	stomach resection	5	17.9	17.9	64.3
	duodenum whipple procedure	2	7.1	7.1	71.4
	jejunum and ileum small bowel resection	3	10.7	10.7	82.1
	rt. hemicolectomy	1	3.6	3.6	85.7
	lt. hemicolectomy	1	3.6	3.6	89.3
	rectum low anterior resection	1	3.6	3.6	92.9
	eosophageal resection and proximal gastrectomy	2	7.1	7.1	100.0
	Total	28	100.0	100.0	

Tumor characteristics

Location

Tumor location most commonly found in stomach 18 cases (64.3%) followed by small bowel 5 cases (17.9%) as shown in table 3.

Table 3

pathology site

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	stomach	18	64.3	64.3	64.3
	duodenum	2	7.1	7.1	71.4
	jejun. and ileum	3	10.7	10.7	82.1
	rt. and lt. colon	2	7.1	7.1	89.3
	rectum	1	3.6	3.6	92.9
	lower eosophagus	2	7.1	7.1	100.0
	Total	28	100.0	100.0	

Size

Tumor size in our study divided in three categories less than 3 cm, 3_5 cm and more than 5 cm in (7, 8 and 13) cases respectively, and in (25, 28.6 and 46.4)% also respectively. As shown in table 4.

Table 4

CT_scan mass size

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	< 3	7	25.0	25.0	25.0
	3_5	8	28.6	28.6	53.6
	>5	13	46.4	46.4	100.0
	Total	28	100.0	100.0	

Histological study

The mitotic index in two types less than 5 in 50 HPF which is found in 14 cases (50%) which is considered low resk, and more than 5 mitotic cells in 50 HPF 14 cases (50%) which is considered high risk, also all cases 28 show immune histochemistry CD117 positive, and the high risk keeped on imatinib treatment. As shown in table 5.

Table 5

histopathology findings

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	< 5 mitotic no. low risk	14	50.0	50.0	50.0
	5 or more mitotic no. high risk	14	50.0	50.0	100.0
	Total	28	100.0	100.0	

Correlations Between Clinical and Pathological Parameters

There is statistically significant correlation between age and mitotic index (p=0.02). Higher mitotic index was correlated with younger age of the patients, as shown in table 6 and figure 5.

Table 6

pt. age * histopathology findings Crosstabulation

Count

		histopathology findings		
		< 5 mitotic no. low risk	5 or more mitotic no. high risk	Total
pt. age	21_30	0	1	1
	31_40	1	6	7
	41_50	1	1	2
	51_60	2	1	3
	more than 60	10	5	15
Total		14	14	28

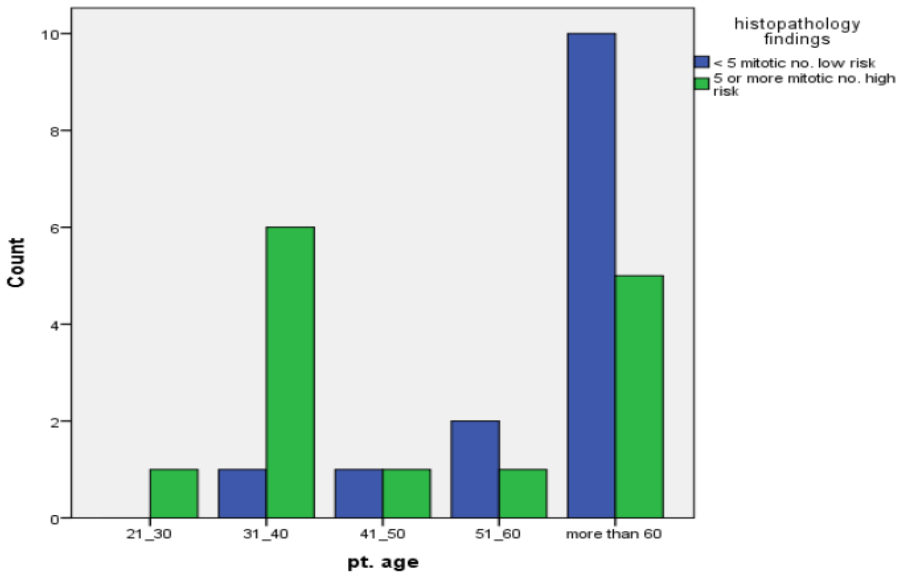

Fig. 5: Correlation age with mitotic index.

Higher MI was also tied with larger tumors and also statistical significant (p<0.001) as shown table 7 and figure 6.

Table 7

CT_scan mass size * histopathology findings Crosstabulation

Count

		histopathology findings		
		< 5 mitotic no. low risk	5 or more mitotic no. high risk	Total
CT_scan mass size	< 3	6	1	7
	3_5	7	1	8
	>5	1	12	13
Total		14	14	28

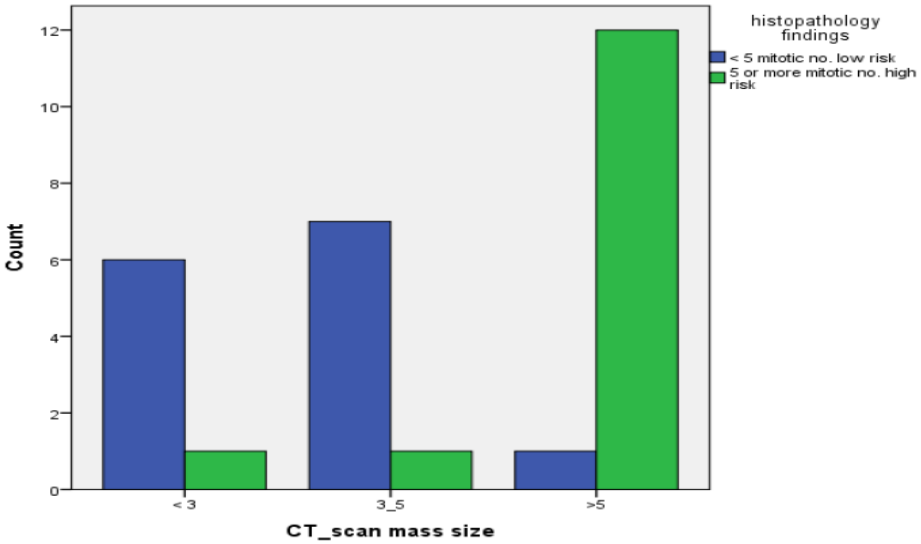

Fig. 6: Correlation size with mitotic index.

Also there is increase in mitotic index in cases non gastric GIST as compared to gastric GIST as shown in table 8 figure 7, but it is not significantly statistic (p=0.66).

Table 8

pathology site * histopathology findings Crosstabulation

Count

		histopathology findings		
		< 5 mitotic no. low risk	5 or more mitotic no. high risk	Total
pathology site	stomach	12	6	18
	duodenum	0	2	2
	jejun. and ileum	1	2	3
	rt. and lt. colon	1	1	2
	rectum	0	1	1
	lower eosophagus	0	2	2
Total		14	14	28

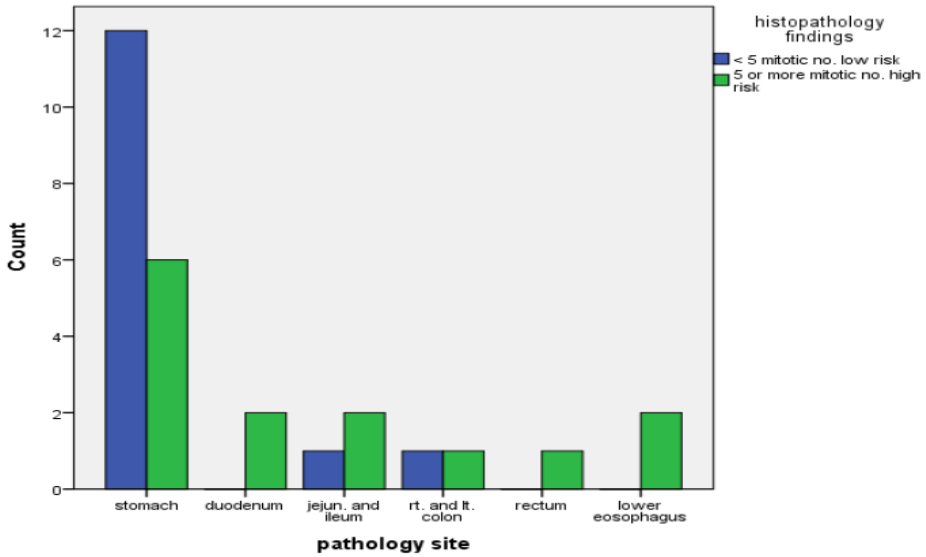

Fig. 7: Pathology Site and Mitotic index.

Surveillance

We followed up our patients for the research duration 2 years all patients have no mortality and no recurence happened, however, a 14 cases high mitotic index treated expectant and imatinib 400 mg. Once daily in oncologist follow up.

DICCUSSION

The most common site of GIST in our study was the stomach, which is in keeping with most clinical reports. The question still remains, is tumor location of any significance as a prognostic factor? Some studies insist that it does,[1,20,21,22-23] while others say it does not hold any statistical relevance.[24-24] Our data correspond more to the latter one. In addition, there is some evidence in the literature that supports gastric location as a positive prognostic factor.[22] Our analysis shows that there is no strong indication that would suggest a correlation between tumor site and its mitotic index (p=0.66). There are numerous studies trying to define a threshold of tumor diameter for its recurrence and/or malignant behavior. For example, some analyses give 10 cm as a cut-off point,[25] while others use 5 cm[11,26] and there are some that go as low as 3 cm..[48] In 2002,[28] Fletcher and his colleagues collaborated to create the NIH (National Institute of Health) classification, the first GIST grading system taking into account tumor diameter and its mitotic activity, thus determining the risk of recurrence. The Appelman and Helwig[29] categorization system reported that the odds of malignant probability increase in tumors of diameter over 50 mm. Our analysis did find this correlation and it pointed out that the larger the tumor, the higher its mitotic index (p<0.0001), which indirectly means higher malignant potential, likewise many studies indicated tumor size as an adverse factor in patients with GISTs.[2,8,21,28,22,30,31-33,24,34-25,35,36] Some studies point out mitotic index as one of the main determinants.[2,8,11,20,21,28,22,30,31,32,37-38,39,25,35] Elderly people tend to have higher incidence rates of the tumor.[28] We found a correlation between mitotic index and age of the patients. The younger the patient, the higher tumor's mitotic index. Age is one of the more controversial topics concerning GISTs survival rates and as its prognostic factor. Some studies indicate that it does not affect it in any way,[20,36] while others consider it as a possible prognostic aspect.[1,21,22,26,31,23] Among those, a few state that younger age tends to be more problematic,[23] while others claim the exact opposite.[26] We decided to divide our patients into 2 groups based on their age, with a 60-year-old threshold. 13 of them were 60 years old or younger, while 15 were over 60 years old. Our analysis points out that younger patients have mitotic index higher. It is, however, It may suggest more aggressive behavior of tumors in younger patients. Potential risk factors such as primary location, tumor diameter, epithelioid type(not spindle), genetic axon mutation and mitotic index varied significantly between the different age groups. However, age itself (without subdividing into different age groups) correlated only with mitotic index (p=0.02). while no relationship between age and tumor primary location (p=0.66). There is slight increase incidence in male patient but it isn't significant (p=0.76) like in (30), other show male bad prognostic factor (20,23) while another said it is increase survival in male gender (25). Results of imatinib use show that this drug is highly effective, especially with non-resectable or high-risk GISTs.[2,8,22,30-32,34] In intermediate-risk GISTs, however, some studies indicate that imatinib adjuvant therapy does not add any significant benefits for the patients[39] while others claim that it does.[41,42] A study suggested neo-adjuvant therapy should be used before surgery in advanced GISTs.[43] In our study, 14- patients were treated with imatinib (Gleevec) in a dose 400 mg. Once daily with oncologist, and We still follow up the patients without recurence or death.

CONCLUSION

We found the following things in our research, there is strong correlation between patient age and tumor size

with high mitotic index which reveal high malignancy ($p=0.02$ and $p<0.001$, respectively), which it's significantly high. Also there is more incidence in male but not significant, and site of the tumor associated with different mitotic incident but it's not significant.

Recommendation

To assess proper approach to GIST we must have MDT, to reach optimal cure of the patients. We must now the aetiology and possible risk factors associated with good or poor prognosis.

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