A Retrospective Study of Postoperative Outcomes in 98 Patients Diagnosed with Gastrointestinal Stromal Tumor (GIST) of the Upper, Middle, and Lower Gastrointestinal Tract Between 2009 and 2019 at a Single Center in Poland

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Background: Gastrointestinal stromal tumors (GISTs) arise in the smooth muscle pacemaker interstitial cells of Cajal, or similar cells. The aim of this retrospective study between 2009 and 2019 from a single center in Poland was to assess the selected prognostic factors (location, tumor size, mitotic index, body mass index (BMI), length of hospital stay, age, sex, and coexistent neoplasm) and to investigate postoperative outcomes in 98 patients with GIST of the upper, middle, and lower gastrointestinal tract.

Material/Methods: Between 2009 and 2019, 98 patients (50 women and 48 men) with an average age of 63.8 years (range from 38 to 90 years) were operated on for GIST in the Department of Gastrointestinal Surgery in Katowice, Poland. Based on the intraoperative and postoperative investigations, the tumor size and mitotic index were determined in each case.

Results: A statistically significant correlation between age and mitotic index (MI) was found (p=0.02). The higher the MI, the younger the age of the patients. However, regardless of sex, younger patients had a tendency to survive longer. A >60-year-old male patient's probability of survival was around 65% after 40 months. Higher mitotic index was also associated with larger tumor size (p<0.0001). Female patients had a tendency to survive longer than males.

Conclusions: The findings from this small retrospective study support the importance of preoperative evaluation and frequent postoperative follow-up for patients with GIST of the gastrointestinal tract, particularly in older male patients, and patients with malignant comorbidities, which are associated with increased mortality.

Keywords: Gastrointestinal Neoplasms · Gastrointestinal Stromal Tumors · Medical Oncology

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Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor located in the gastrointestinal (GI) tract [1]. Most studies have reported the incidence of clinically relevant GISTs at 10-15 per million population 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%) [2,3]. In very rare circumstances, GISTs appear outside of the gastrointestinal tract – they are called extra-gastrointestinal stromal tumors (eGIST) [4]. GISTs occurring outside of the stomach are associated with a higher malignant potential [5]. Gastrointestinal stromal tumors were originally believed to originate from the mesenchymal cells of the gastrointestinal tract [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 mm^2 or per 50 high-power field (HPF)) and high grade (>5 mitoses per 5 mm^2 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

[9,13,14]. 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 [15]. 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 [9,16]. Some GISTs express or gain resistance to both drugs [9]. In recent years, regorafenib was introduced as a third-line treatment [9,17-19]. The current NCCN treatment recommendations for localized resectable disease include surgical resection for gastric tumors <2 cm with no high-risk features and periodic endoscopic or radiographic surveillance. After complete resection, treatment with adjuvant imatinib is recommended, with follow-up history and physical examination and abdominal/pelvic CT every 3 to 6 months for 5 years, then annually [12].

Conflicting reports about the different clinical and histopathological factors affecting prognosis in patients with GIST have emerged [11,20-24]. Therefore, this retrospective study between 2009 and 2019 from a single center in Poland aimed to investigate postoperative outcomes and selected prognostic factors in 98 patients diagnosed with gastrointestinal stromal tumor (GIST) of the upper, middle, and lower gastrointestinal tract.

Material and Methods

Ethics Statement

This was a retrospective study of medical records and all data were fully anonymized before we accessed them. Written informed consent was obtained from all participants. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Our study is exempted from institutional review board (IRB) approval according to local legislation [25]. Only a medical experiment needs to obtain ethical approval, and a retrospective study including analysis of patients' medical records does not need IRB approval.

Diagnosis of GIST

Patients were diagnosed, treated, and monitored after the surgery according to current ESMO guidelines [9]. 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, smooth muscle actin (SMA), and S-100 protein were carried out to differentiate between GISTs and other mesenchymal neoplasms. They were completed in the Department of Pathology, Medical University of Silesia, Katowice, Poland. 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 comorbidities).

Patients' Characteristics

Between 2009 and 2019, 98 consecutive patients (50 women and 48 men) with an average age of 63.8 years (range from 38 to 90 years) were operated on for GIST in the Department of Gastrointestinal Surgery Medical University of Silesia, Katowice, Poland.

Management of GIST

Patients with a locally advanced, resectable tumor (without distant metastases) with an acceptable perioperative risk were qualified for elective surgery. In case of tumor hemorrhage or rapture, patients were qualified for urgent surgery due to vital indications. Some tumors were found intraoperatively during surgery performed for a different reason. 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 3 groups according to location within the gastrointestinal tract: (1) upper gastrointestinal tract (UGIT) – esophagus, stomach, duodenum; (2) middle gastrointestinal tract (MGIT) – jejunum and ileum; and (3) lower gastrointestinal tract (LGIT) – colon, rectum, and others. The tumor size cut-off point was decided to be 50 mm [11]. The mitotic index (MI), defined as the number of mitotic figures in 50 high-power fields (HPF), was assessed. We decided to divide it into 3 groups: A (0-1), B (2-9), and C (≥10). The patients were split into 2 age groups (≤60 years old or >60 years old). The duration of postoperative hospitalization ranged from 5 to 72 days (mean 14 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 (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, rectal location, or applied adjuvant chemotherapy (imatinib), additional chest X-ray every year was conducted. Thirty-three patients are lost to follow-up and were excluded from several analyses.

Evaluation of Patient Outcome

The malignant potential of GISTs was categorized according to the Appelman and Helwig classification [27]. In addition, we stratified patients based on National Institute of Health (NIH) consensus criteria for GIST risk according to Fletcher et al [28,29].

Statistical Analysis

Detailed descriptive analysis was performed. Correlation between sex, age, tumor location, mitotic index, tumor size, body mass index (BMI), length of hospitalization, coexistent neoplasm, imatinib treatment and survival of patients was assessed. Results were subjected to statistical analysis, where $p<0.05$ was considered to be significant. Univariate and multivariate survival analysis was performed. Survival curves were calculated applying the Kaplan-Meier method. Breslow hazard functions were applied and its use is shown in figures in order to handle patients lost to follow-up. The Breslow estimator was used to determine the cumulative baseline hazard function, which allowed the application of simple statistical transformations [30]. Confidence intervals (CI) were determined at the 95% level. We also calculated the risk of GIST recurrence based on GIST Risk Calculator, which is formed by research from Dr. Heikki Joensuu, Professor of Oncology at the University of Helsinki and the Research Director at the Helsinki Comprehensive Cancer Center, and his colleagues [31]. The study encompassed an international sample of 2000 diagnosed GIST patients, and analyzed them using a mathematical model designed by Professor Aki Vehtari of Aalto University. It 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 26.

Results

Surgical Treatment

There were numerous surgical procedures used in the study (Table 1). Surgical approach depended on the tumor location, size, and the prospect of complete resection. A wedge gastric excision was the most frequent surgical procedure (42.86%).

Table 1. Surgical procedures and tumor location (n=98*).

Gastric wedge resection	42	(42.86%)
Partial gastric resection	22	(22.45%)
Duodenal resection	10	(10.20%)
Pancreatoduodenectomy	6	(6.12%)
Total gastric resection	6	(6.12%)
Partial intestinal resection	5	(5.10%)
Local intestinal resection	3	(3.06%)
Transhiatal esophageal resection	2	(2.04%)
Right hemicolectomy	1	(1.02%)
Transverse colon resection	1	(1.02%)
Stomach	70	(71.43%)
Duodenum	10	(10.20%)
Jejunum and ileum	8	(8.16%)
Pancreas	6	(6.12%)
Oesophagus	2	(2.04%)
Large intestine	2	(2.04%)

* Number of patients.

Patient Characteristics

The study group consisted of 50 (51.02%) men and 48 (48.98%) women, with a mean age of 63.8 (±10.6) years (range 38-90) (**Table 2**). Sixty-two patients (63.3%) were aged >60 years.

Tumor Characteristics

Tumor Location

Tumor characteristics are presented in **Table 3**. Eighty-two patients (83.7%) had tumors located in the UGIT, while only 2 (2%) were in the LGIT. Eight cases were detected in MGIT (**Table 3**). The stomach was the most prevalent location (71.4%) (**Table 1**). Thirty UGITs were found in the ≤60-year-old group, while 52 UGITs were in the >60 years group (**Table 3**). Significantly more MGITs were found in the >60 years population (6 vs 2).

Tumor Size

The mean tumor size was 57 (±49) mm (3-240), and a neoplasm diameter ≥5 cm was discovered in 45 patients (45.9%) (**Table 2**). Mean tumor diameter in UGITs were found to be

Table 2. Patient and tumor characteristics (n=98*).

	F	M	Together
Average age	64.12	63.46	63.8 (±10.6)
Number of patients	50 (51.02%)	48 (48.98%)	98
Mitotic Index (/50 HPF) (n=98)**			
Mean (range)		5.19 (±7.95) (0-44)	
A (0-1)		27 (27.55%)	
B (2-9)		61 (62.24%)	
C (≥10)		9 (9.18%)	
Unknown		1 (1.02%)	
Risk of malignant behavior (n=98)			
Very low		17 (17.35%)	
Low		33 (33.67%)	
Intermediate		23 (23.47%)	
High		24 (24.49%)	
Unknown		1 (1.02%)	
Tumor size [mm] (n=97)			
Mean (range)		57 (±49) (3-240)	
<50 mm		52 (53.61%)	
≥50 mm		45 (46.39%)	

* Number of patients; ** High-Power Field.

Table 3. Tumor characteristics (division into groups) (n=92*).

	Location		
	Upper gastrointestinal tract	**Middle gastrointestinal tract**	**Lower gastrointestinal tract**
MI**			
0-1	21 (25.61%)	4 (50%)	0 (0%)
2-9	53 (64.34%)	3 (37.5%)	2 (100%)
>9	8 (9.76%)	1 (12.5%)	0 (0%)
Total	82	8	2
Age			
≤60	30 (36.59%)	2 (25%)	1 (50%)
>60	52 (63.31%)	6 (75%)	1 (50%)
Total	82	8	2
Tumor size			
Mean	56.2 (±47.6) mm	48.1 (±48.1) mm	57.5 (±17.7) mm
≤50	49/82 (59.76%)	7/8 (87.5%)	½ (50%)
>50	33/82 (40.24%)	1/8 (12.5%)	½ (50%)
Total	82	8	2

* Number of patients; ** mitotic index.

Table 4. Tumor characteristics: National Institute of Health classification and tumor location within the gastrointestinal tract (n=92*).

National Institute of Health	Very low risk	Low risk	Medium risk	High risk
Location	Mitotic index ≤5 Size <20 mm	Mitotic index ≤5 Size ≥20 ≤50 mm	Mitotic index ≤5 Size ≥50 ≤100 mm	Mitotic index ≤5 Size >50 mm
			Mitotic index ≥6 ≤10 Size ≤50 mm	Mitotic index >10 Size >100 mm
Upper gastrointestinal tract (n=82)	14 (17.07%)	26 (31.71%)	21 (25.61%)	21 (25.61%)
Middle gastrointestinal tract (n=8)	2 (25.00%)	4 (50.00%)	1 (12.50%)	1 (12.50%)
Lower gastrointestinal tract (n=2)	0 (0.00%)	1 (50.00%)	1 (50.00%)	0 (0.00%)

* Number of patients

56.2 (±47.6) mm, while in MGIT was 48.1 (±48.1) mm and LGIT was 57.5 (±17.7) mm (**Table 3**). Sixty percent of patients had ≤50 mean neoplasm size, whereas 40% of patients had >50 mean tumor size in the UGIT category.
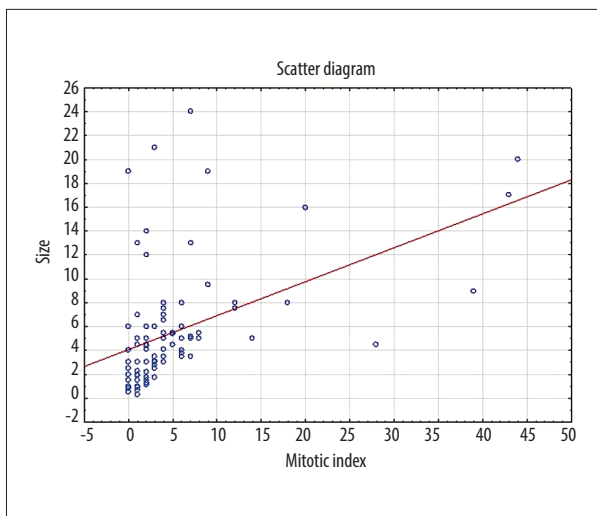
Tumor mitotic index

The mean MI was 5.19 (±7.95) HPF (0-44) and a MI ≥10/50 HPF was noted in 9 patients (9.2%). Twenty-seven patients (27.6%) had MI from 0 to 1. The largest group consisted of 61 patients (62.2%), and their MI ranged between 2 and 9 (**Table 2**). Low-risk GISTs, according to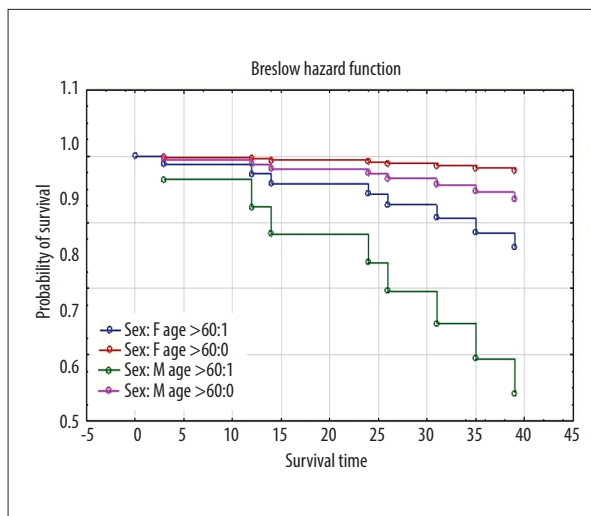 NIH classification, were the most common (34.02%), followed by high- (24.74%), intermediate- (23.71%), and very low-risk (17.53%) (**Table 4**). Fifteen (15.3%) patients had coexisting additional malignant neoplasms. Five of them had adenocarcinomas, while the others had different types of gastric or pancreas tumors.

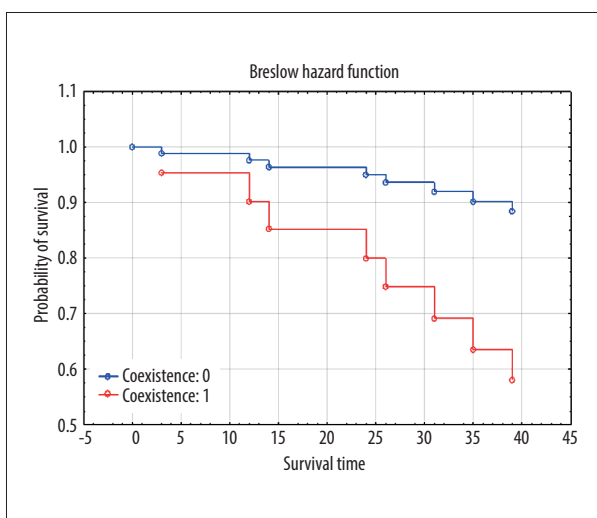**Correlations Between Clinical and Pathological Parameters**

Data analysis (**Table 5**) showed a statistically significant correlation between age and mitotic index (p=0.02). Higher mitotic index was correlated with younger age of the patients. Higher MI was also tied with larger tumors (p<0.001) (**Figure 1**).

Figure 1. Scatter diagram shows correlation between Mitotic Index and size of the tumors.

Figure 2. Breslow hazard function demonstrates the difference in probability of survival between patients with and without coexisting neoplasm after certain time.

Other correlations worth noting exist between length of hospitalization, mitotic index, and tumor diameter (the higher index and larger tumor, the longer the hospital stay (p=0.148 and p=0.277, respectively), as well as age and tumor size (the bigger the size, the younger the age (p=0.233) although they were not statistically significant (p<0.05 was considered to be significant).

Survival Analysis

Among the 98 operated patients, long-term postoperative follow-up was performed in 60 of them (61.22%). The mean overall survival (OS) was 57.03 (±36.29) months (3-123). Seven patients died during the follow-up period due to various causes

Figure 3. Breslow hazard function shows the difference in probability of survival between different age groups and sexes in time.

(disease progression, cardiovascular disorders, cerebral stroke). Another 2 deaths occurred shortly after surgery due to postoperative complications. We found a correlation between survival and coexistence of additional neoplasm (n=15). In patients with coexisting tumors, the chance for survival after 39 months was 58%, while in the absence of additional neoplasm it was 88% (**Figure 2**). Furthermore, as these Breslow hazard functions show (**Figure 3**) (p<0.05), there is a strong relationship between sex in different age groups and their survival time. Female patients under the age of 60 had a 97.5% chance for survival after 39 months, while those at the age of 60 or above had 86% chance. However, male patients under the age of 60 had a 93% chance to be alive while those 60 years and older had only a 63% chance for survival.

Discussion

The most common site of GIST in our study was the stomach. There was no correlation between tumor site and mitotic index (p=0.572) or size (p=0.778). A larger tumor was associated with a higher mitotic index (p<0.0001). We also found a correlation between mitotic index and age of the patients. The younger patient's age was correlated with the higher tumor mitotic index. The age was correlated only with mitotic index (p=0.02), while a relationship between age and tumor primary location (p=0.495) or size (p=0.233) was not found. Male sex was the strongest poor prognostic factor in patients with GISTs. There was no statistically significant correlation between patient's sex and tumor primary location (p=0.512), mitotic index (p=0.786), or size (p=0.951). Body mass index (BMI) did not influence OS or disease-free survival (DSF), and its correlation with tumor primary location (p=0.615), mitotic index

**Table 5.** Correlations between clinical and pathological parameters (n=98*).

	Location	Mitotic Index	Size
Sex	-0.0693	0.0280	-0.0063
	p=0.512	p=0.786	p=0.951
Age	-0.0721	-0.2368	-0.1222
	p=0.495	p=0.020	p=0.233
Body mass index	0.0531	0.0432	-0.0164
	p=0.615	p=0.674	p=0.873
Hospital stay	-0.0074	0.1480	0.1114
	p=0.944	p=0.148	p=0.277
Location	1.0000	-0.0597	-0.0300
	p=---	p=0.572	p=0.778
Size	0.0300	0.4704	1.0000
	p=0.778	p<0.0001	p=---

* Number of patients.

(p=0.674), and size (p=0.873) was not significant (**Table 5**). In our study, length of hospital stay did not correlate with OS, DFS. There was no correlation between length of hospital stay and tumor primary location (p=0.944), mitotic index (p=0.148), or size (p=0.277). There was a very significant correlation between coexistence of the other malignant neoplasm and probability of survival in our patients (p<0.001).

The most common site of GIST in our study was the stomach, which is in keeping with most clinical reports [3,20,32-34]. The question still remains, is tumor location of any significance as a prognostic factor? Some studies insist that it does [1,20,21,32-42], while others say it does not hold any statistical relevance [43-47]. 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 [32]. Our analysis shows that there is no strong indication that would suggest a correlation between tumor site and its mitotic index (p=0.572) or size (p=0.778).

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 [47], while others use 5 cm [11,33] 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 [27] categorization system reported that the odds of malignant probability increase in tumors of diameter over 60 mm. Our analysis did not find this correlation, however; it pointed out that the larger the tumor, the higher its mitotic index (p<0.0001),
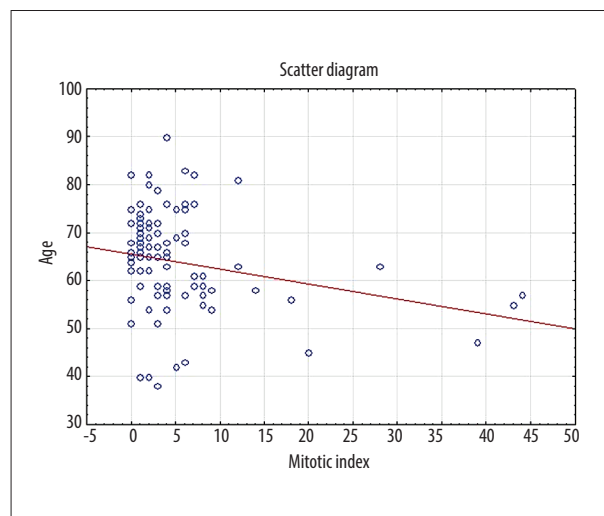
Figure 4. Scatter diagram displays correlation between mitotic index and age of the patients.

which indirectly means higher malignant potential (**Figure 1**). Many studies indicated tumor size as an adverse factor in patients with GISTs [2,8,21,28,32,36,38-40,43,45-47,49,50]. Some studies point out mitotic index as one of the main determinants [2,8,11,20,21,28,32,36, 38,39,41-44,46,47,49]. We found a correlation between mitotic index and age of the patients. The younger the patient, the higher tumor's mitotic index (**Table 5, Figure 4**).

The association between the most frequent poor prognostic factors and survival in patients with GISTs in the recent literature is shown in **Table 6**.

Table 6. Association between the most common poor prognostic factors and survival in patients with Gastrointestinal stromal tumors (GISTs) in the recent literature (2009-2018).

Author (publication year)	n	Age	Gender	Location	Size, cm	MI*/50 HPF**	Others
Unalp HR (2009) [27] (33)	41	ns***	ns	nd****	ns	ns	IR*****
Huang CC (2009) [55] -45(51)	70	nd	nd	Small intestine	Large	High	
Zhang Y (2009) [56]-46(52)	181	ns	ns	ns	Large	ns	Advance
Cao H (2010) [30] (36)	181	ns		ns	large	ns	Advance
Huang H (2010) [43] (49)	187	nd	nd	Upper stomach	ns	ns	IR, grading
Fan R (2011) [57] -47 (53)	114	nd	nd	ns	Large	ns	
Euanorasetr C (2011 [58] -48 (54)	32	nd	nd	nd	nd	>5	
Mrowiec S (2012) [17] (20)	105	nd	Male	Non-gastric	nd	≥10	Co-ex neoplasm
Zgang P (2012) [38] (44)	217	nd	nd	nd	nd	High	Metastasis
Wu XJ (2012) [39] (45)	337	nd	nd	nd	Large	nd	IR, metastasis
Rosa F (2012) [59] -49(55)	50	nd	nd	nd	>10	High	Rupture
Yen CC (2012) [60] -50 (56)	142	nd	nd	Non-gastric	Large	High	AURKA ****** exp.
Ning L (2013) [32] (38)	247	ns	nd	ns	Large	High	Rupture
Wang M (2014) [40] (46)	497	nd	ns	nd	Large	High	Grading
Feng F (2017) [41] (47)	114	nd	nd	Mesenteric	>10	>5	Grading
Liu X (2018) [26] (32)	2570	≥60	ns	Non-gastric	>5	>5	IR
Yang ML (2018) [61] -51 (57)	182	nd	nd	Non-gastric	ns	High	Metastasis

* Mitotic index; ** High-Power Field; *** not significant; **** not dependent; ***** incomplete resection; ****** gene.

Elderly people tend to have higher incidence rates of the tumor [28]. 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 [20,50], while others consider it as a possible prognostic aspect [1,21,32,33,38,42]. Among those, a few state that younger age tends to be more problematic [42], while others claim the exact opposite [33]. We decided to divide our patients into 2 groups based on their age, with a 60-year-old threshold. Thirty-three of them were 60 years old or younger, while 59 were over 60 years old. Our analysis points out that younger patients have longer OS (**Figure 3**) and mitotic index is also higher. It is, however, an outlier in comparison to other studies (**Figure 4**). It may suggest more aggressive behavior of tumors in younger patients. Potential risk factors such as primary location, tumor diameter, 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=0.495) or size (p=0.233) was found (**Table 5**).

In our study, male sex was the strongest poor prognostic factor in patients with GISTs. Their survival rate was at a significantly lower level than in females, regardless of age. However, the difference is most striking in the group over 60 years old (**Figure 3**). This is in line with some previous studies [20,42]. It is worth mentioning that there is one paper that suggests that it does not matter [36] and one that suggests that male sex increases survival rates [33]. It is, however, an outlier, and Cox proportional hazards model does not support univariate analysis in this case. There was no statistically significant correlation between sex and tumor primary location (p=0.512), mitotic index (p=0.786), or its size (p=0.951) (**Table 5**).

Body mass index (BMI) is one of the basic clinical parameters that is being included in clinical studies. With the general population getting more and more obese [58,59], an analysis

regarding its significance as a prognostic factor needed to be done. It has not been reported in the literature. Our research shows that it does not influence OS or disease-free survival (DSF) and its correlation with tumor primary location (p=0.615), mitotic index (p=0.674), and size (p=0.873) is not significant (**Table 5**).

Length of hospital stay as a prognostic factor is another important topic that is not discussed in the literature. Our study shows that it does not correlate with overall survival or disease-free survival, and it is not significantly correlated with tumor primary location (p=0.944), mitotic index (p=0.148), or size (p=0.277) (**Table 5**).

Coexisting neoplasms in patients with GISTs are fairly common [60], and occur in 2.95-33.33% of cases. It occurred in 15 (15.31%) of our patients. Analysis reveals that there is a very significant correlation between coexistence of the other malignant neoplasm and probability of survival (**Figure 2**) (p<0.001). In patients with coexisting tumors, the probability of survival beyond 39 months was 58%, while in the absence of additional neoplasm it was 88%. Additional tumors are most frequently found in the stomach [61]. Our data confirm these findings, although it is worth noting there were several tumors located in the pancreas. There is little evidence of the coexistence of the other neoplasm as a prognostic factor in patients with GISTs [20,62]. Some studies have assessed the occurrence, clinicopathology, epidemiology, immunohistochemical analysis, and treatment of GISTs coexisting with other malignant neoplasms [61,62]. Sometimes GISTs appear in groups [63].

We also calculated risk of GIST recurrence based on GIST Risk Calculator, which was formed by research from Dr. Heikki Joensuu, Professor of Oncology at the University of Helsinki and the Research Director at the Helsinki Comprehensive Cancer Center, and his colleagues [31]. The study encompassed an international sample of 2000 diagnosed GIST patients, and analyzed them using a mathematical model designed by Professor Aki Vehtari of Aalto University. It 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. In our study the chance of recurrence after 5 and 10 years was 22.32% and 28.49%, respectively, without taking into account so-called "low risk" tumors. Low-risk tumors, according to the calculator, are those with a chance of recurrence lower than 1%. If we take them into account as well (counting them as a 0.5% chance of recurrence on average), median risk drops to 18.19% and 24.13%, respectively.

Results of imatinib use show that this drug is highly effective, especially with non-resectable or high-risk GISTs [2,8,32,36-39,45]. In intermediate-risk GISTs, however, some studies indicate that imatinib adjuvant therapy does not add

any significant benefits for the patients [64] while others claim that it does [65,66]. A study suggested neo-adjuvant therapy should be used before surgery in advanced GISTs [67].

In our study, 9 patients were treated with imatinib (Gleevec), and the sample size was not large enough to determine any statistical significance.

There are some limitations to our research. It was a single-center retrospective study and it was restricted to 98 patients. There may be some bias that could have been introduced by the long duration of the study. Some data were not available, as in another retrospective studies. Some of the material was insufficient for proper statistical analysis (for example, the imatinib use).

Conclusions

There is an association between tumor location, size, length of hospital stay, and survival of patients with GISTs. The larger tumors and tumors with higher mitotic index were associated with longer hospital stay (p=0.277 and p=0.148, respectively). Larger tumors also coincided with younger age (p=0.233). Significant correlations between the mitotic index, age, and size were noted. A higher mitotic index was associated with younger age and larger size (p=0.02 and p<0.001, respectively). Female patients tended to survive longer than males. Younger patients had longer OS. The findings from this small retrospective study support the importance of preoperative evaluation and frequent postoperative follow-up for patients with GIST of the gastrointestinal tract, particularly in older male patients and in patients with malignant comorbidities, which are associated with increased mortality. The findings from this study support the recommendations from current clinical guidelines.

Institutional Review Board Statement

Data Availability Statement

Conflicts of Interest

None declared.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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