ORIGINAL PAPERS

Adv Clin Exp Med 2014, **23**, 4, 567–573
ISSN 1899–5276

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The Clinical and Histopathological Factors in Patients Operated on for Gastric GIST Tumors with Unclear Diagnosis

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. The preoperative radiological diagnosis of GIST is complicated by its varied macroscopic morphology. Moreover, the precision of preoperative histopathological diagnostics is reduced by the submucosal localization of the lesion.

Objectives. The goal of the study was to perform a retrospective analysis of the clinical and histopathological factors seen in patients operated on for a stomach GIST tumor with unclear diagnosis.

Material and Methods. Two groups of GIST patients treated in our department were compared with regard to their histopathological and clinical data. The first group (9 patients, group 1) comprised patients with a histopathological diagnosis for stomach GIST confirmed before the surgical procedure, while the second group (10 patients, group 2) comprised patients with no solid histopathological diagnosis before surgery. The following clinical and histopathological variables were analyzed in the study: age, gender, presence or absence of metastases, anatomical location of metastases, symptoms, tumor size, surgical mortality, tumor recurrence, treatment with imatinib, patient survival in months, histological subtype, mitotic index, cellular atypia, necrosis, tumor ulceration and Ki-67. The results were analyzed statistically.

Results. The mean survival time differed significantly between the two study groups: group 1 being 12 months and group 2 being 8 months. The lower survival time in group 2 was connected with the higher stage of the disease at the moment of diagnosis.

Conclusions. Our findings suggest that GIST tumors with an unclear diagnosis are recognized at a late stage of the disease. The more advanced stage of the tumor probably results from faster tumor growth caused by higher proliferation activity. These GIST tumors are characterized by a lower survival rate due to the later stage of the disease at the time of diagnosis (**Adv Clin Exp Med 2014, 23, 4, 567–573**).

Key words: gastric GIST tumor, difficult diagnostic GIST, difficulties in diagnosis.

Gastrointestinal stromal tumors (GIST) occur in only roughly 2% of gastric neoplasms [1]. However, GISTs have recently become the most common mesenchymal malignancies diagnosed in the stomach [2]. The stomach is also the most common location of gastrointestinal GIST (60% of cases) [3]. The annual incidence of GIST is estimated between 1 and 2 cases per 100000 population [4].

The malignant transformation of interstitial Cajal cells has been proven to be crucial for GIST development. As the molecular background of the neoplastic changeover of Cajal cells is believed to be a mutation of the c-KIT proto-oncogene [5], GIST is diagnosed by immunostaining the CD 117 (KIT) antigen expressed on the tumor cells, although it then must be differentiated from other mesenchymal tumors [6]. The CD 117 protein is a mutated membrane receptor tyrosine kinase that acts as a target for modern adjuvant GIST therapy. Imatinib is the substance that inhibits the tyrosine kinase receptor, thereby inhibiting proliferation and promoting tumor apoptosis [7]. However, although imatinib has changed the treatment possibilities for GIST patients, surgical resection remains

a key method in GIST management [8]. Radiotherapy is not in common use as a treatment for GISTs and is suggested only in selected cases [9].

Size and mitotic index have been identified as risk factors in GIST malignancy [10]. Other features, such as location, proliferation index and mutation type, are suggested to influence the presence or absence of metastases, and recurrence of tumors [10]. Many risk scores (e.g. NIH criteria, AFIP criteria) have been formulated regarding the above-mentioned factors, enabling the prediction of tumor recurrence, metastases and survival [11].

GISTs present a wide range of clinical manifestations from totally asymptomatic to symptoms typical of the malignancy (e.g. weight loss, abdominal tumor) [3]. Some authors estimate that 15–30% of GIST tumors are asymptomatic and discovered incidentally [4, 12, 13]. The most commonly used imaging methods for GIST diagnosis are ultrasonography and computer tomography [14], while PET/CT is used more for monitoring the course of treatment than for diagnosis [15]. The preoperative radiological diagnosis of GIST is complicated by its diverse macroscopic morphologies [16]. Some authors speculate that it is hard to determine the origin organ of a GIST tumor larger than 3 centimeters [13]. Preoperative histopathological diagnostics appear to be imprecise when the lesion is located in the submucosal area, in which case the specimen collected during biopsy is often nondiagnostic [17]. Therefore, only 15% of individuals are suspected of being GIST patients prior to the operation [18].

The literature about GIST tumors with obscure diagnoses is poor, and no analysis of the survival rate of patients with the condition could be found.

Patients and Methods

The goal of the study was to perform a retrospective analysis of clinical and histopathological factors in patients operated on due to stomach GIST tumors which presented difficult diagnoses. The present retrospective study analyzes a number of anathomopathological and clinical factors seen in patients operated on for GIST tumors in the stomach, over a period of 10 years. Two groups of GIST patients treated in our department were compared, with regard to histopathological and clinical data. The first group (group 1) consisted of patients with a histopathological diagnosis for stomach GIST confirmed before the surgical procedure, while the second group comprised those operated on without a solid histopathological diagnosis before surgery.

Patients

From 2001 to 2010, 19 patients (10 women, 9 men) received a laparotomy due to stomach GIST or suspected stomach GIST tumor. In each patient, an endoscopy was carried out preoperatively with tissue sample collection or core needle biopsy.

A group of 9 patients (group 1) was composed of individuals with preoperative proof of stomach GIST, diagnosed by tissue sample collection during endoscopy. The GIST tumors diagnosed preoperatively were located in the stomach.

The remaining individuals (10 patients) were enrolled to group 2. These subjects were not found to be GIST patients during histopathological diagnosis based on tissue sample collection or core needle biopsy during endoscopy. The patients whose preoperative histopathological diagnosis suggested other neoplasms were excluded from the analysis. Other exclusion criteria were the primary localization of the tumor being elsewhere than the stomach as indicated by preoperative diagnostics (endoscopy and/or computer tomography and/or ultrasonography) or a previous history of abdominal malignancy.

Clinical Parameters

The following clinical variables were analyzed in the study: age, gender, presence or absence of metastases, anatomical location of metastases, symptoms, tumor size, surgical mortality, tumor recurrence, treatment with imatinib, patient survival in months.

Histopathological Parameters

The tumor samples were conventionally inserted in 10% neutral formalin, embedded in paraffin and then deparaffinized. Finally, the histopathological sections were stained with hematoxylin–eosin for further evaluation.

The following histopathological variables were evaluated: histological subtype (fusocellular, epithelioid, or mixed), mitotic index, cellular atypia (low, moderate, and high), necrosis, tumor ulceration and Ki-67 (proliferative index).

Statistical Analysis

The results were presented as mean values and were analyzed using the chi-squared test, analysis of variance and Fisher's test with revision for a small sample group. The power of correlation between the results was assessed by Pearson's correlation coefficient (r). Furthermore, the survival rates were compared using Kaplan-Meier curves

and the log-rank test. P values < 0.05 were considered statistically significant. All statistical analyzes were done using Statistica 10 PL (StatSoft, Tulsa, USA).

Results

Characteristics of the Patients

The clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 62.3 (from 45 to 82 years). All patients of group 1 were clearly symptomatic, mostly with upper gastrointestinal bleeding and dysphagia. Two of these patients presented gastrointestinal bleeding and abdominal pain simultaneously at the time of diagnosis. Although all patients in group 2 were also symptomatic, an abdominal tumor was the first and only symptom of GIST in sixty percent of them. Gastrointestinal bleeding was significantly more common in patients of group 1, while abdominal tumors were significantly more common in group 2. No other statistically significant differences were seen between the groups regarding other clinical symptoms.

Histopathological and Immunohistochemical Characteristics

The histopathological and immunohistochemical features are shown in Table 2. At the time of diagnosis, the metastases were noted in 70% of group 2 compared to 44% of group 1 (statistically significant, $p < 0.05$). Tumor size was significantly greater in group 2 (2.3 cm vs. 6.2 cm; $p < 0.05$).

Ki-67 expression was significantly higher in group 2 (70% vs. 33%, $p < 0.05$). Elevated Ki-67 expression was associated with high mitotic index and high histological grade ($p < 0.05$). High Ki-67 index was associated with low survival. Tumor necrosis and intense cellular atypia tended to be more common in group 2, although this tendency was not found to be significant.

The metastases were located in the liver and peritoneum in both groups.

Survival

No patients from either study group died in the perioperative period. The maximal follow-up time of some analyzed patients was 38 months. The two-year survival rate varied significantly between both groups and was 66.66% and 10%, respectively (95% CI = 19.2–32.3 and 95% CI = 6.3–24.2) (Fig. 1).

The mean survival time differed significantly between the two study groups. The mean survival in group 1 was 12 months, compared to 8 months in group 2 (95% CI = 4.2–13.3 and 95% CI = 2.3–9.2).

All patients in group 1, and only 3 individuals in group 2, received adjuvant therapy with imatinib. The survival difference among group 2 between patients treated with imatinib and patients without adjuvant therapy was not statistically significant.

Complete resection (R0) was feasible in 5 patients of group 1 and, among those, GIST recurrence occurred in 3 cases. Complete resection (R0) was achieved by partial resection in 3 patients of group 1, and total gastrectomy in 2 of group 1.

Radical resection (R0) was performed in only 3 individuals of group 2. In all patients of group 2, the GIST recurrence rate was 100%, despite total gastrectomy being performed.

Discussion

GISTs may present a wide spectrum of biological activity from totally indolent to highly malig-

Table 1. Patient characteristics

	Group 1	Group 2	p value
Age (years) ± SEM	61.2 ± 4.3	63.5 ± 3.9	p not significant
Gender			p not significant
female	6	7	p not significant
male	3	3	p not significant
Clinical symptoms:			
gastrointestinal bleeding	6 (66.66%)	3 (30%)	$p < 0.05$
abdominal tumor	0 (0%)	6 (60%)	$p < 0.05$
dysphagia	2 (22%)	0 (0%)	p not significant
others (weight loss, vomiting, pain)	1 (11%)	1 (10%)	p not significant

Table 2. Clinical and histopathological features

	Group 1	Group 2	p value
Tumor size	2.3 cm	6.2 cm	$p < 0.05$
Presence of metastases	4 (44.44%)	7 (70%)	$p < 0.05$
Mitotic index ≤ 5/50 > 5/50	 7 (77.77%) 2 (22.22%)	 (20%) 8 (80%)	$p < 0.05$
Ki-67 < 10% > 10%	 6 (66.66%) 3 (33.33%)	 (30%) 7 (70%)	$p < 0.05$
Necrosis and/or ulceration	4 (44.44%)	7 (70%)	p not significant
Histological grade: high moderate low	 3 (33.33%) 5 (55.55%) 1 (11.11%)	 7 (70%) 3 (30%) 0 (0%)	p not significant
Cellular atypia: low moderate high	 3 (33.33%) 4 (44.44%) 2 (22.22%)	 2 (20%) 4 (40%) 4 (40%)	p not significant
Histopathological subtype: fusocellular epithelioid mixed	 4 (44.44%) 3 (33.33%) 2 (22.22%)	 3 (30%) 3 (30%) 4 (40%)	p not significant

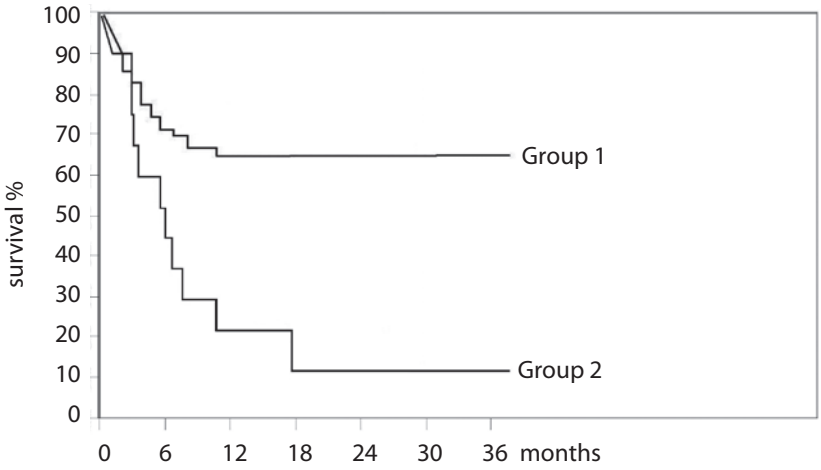

Fig 1. Survival curve

nant. Molecular targeted therapy has changed the treatment and prognosis for GIST patients, though surgical resection remains a key therapy. However, total R0 resection has a significant influence on treatment outcome (survival) and is attained in approximately 40% of all cases of GIST [8]. The type of surgical procedure depends on tumor location and size. However, the main goal of the surgery is the achievement of negative margins. Thus, local resection of GIST lesions is recognized as a gold standard for surgical treatment [19]. Although all patients from our study groups were treated surgically, R0 resection was completed in only approximately 55% of group 1 and in 20% of group 2. The reason for the incomplete resection in a high number of patients was the advanced stage of the disease at the moment of diagnosis. Two factors which influence survival are GIST tumor size and the presence of a negative microscopic surgical margin. In some situations, it is necessary to perform a more extensive procedure to achieve microscopic negative margins [20].

Recent publications have shown complete resection in 40–60% of operated patients [10, 21, 23]. However, the mean tumor size given in these studies was 1.5–4.5 cm, compared to 2.3–6.5 cm in the present study. Moreover, the mitotic index was significantly lower in the above-mentioned studies compared to the present study.

It is estimated that approximately 15–30% of GIST patients are asymptomatic with incidental findings of GIST [4, 12, 13]. In our study, all patients were symptomatic, mostly with gastrointestinal bleeding, and no GIST case was discovered incidentally. Most frequent clinical manifestations described in the literature are gastrointestinal bleeding, abdominal pain, weight loss, abdominal tumor, dysphagia, nausea and vomiting [12]. Its symptoms and incidence in our patients did not vary significantly from the literature data.

Statistical studies indicate that most patients with gastric GIST are 60–70 years old [24, 25]. In our study, the mean age of patients was within the above-mentioned range and no patients were younger than 45 years old.

A variety of problems can potentially be involved in the preoperative diagnosis of gastrointestinal stromal tumors, some of which result from the low incidence of GIST and limited experience of clinicians and radiologists. However, the main reason for a lack of a final preoperative histopathological diagnosis is the diversity of macroscopic GIST morphologies [13, 26]. Nowadays, due to its high availability, the first diagnostic of abdominal symptoms is ultrasonography. An ultrasound image of GIST usually shows a hypoechogenic lesion.[27] However, while the echogenic pattern of a small tumor is homogeneous, the pattern of a larger lesion is heterogeneous. The variety of ultrasound GIST images comprises a wide range of images including cyst, solid tissue or both in one tumor. The establishment of the exact GIST organ of origin is usually difficult in cases where the tumor size is greater than 3 cm [13, 27]. In addition, the possibility of detecting GIST lesions of the gastrointestinal tract by ultrasound scans is significantly reduced because they develop inside the wall. However, ultrasonography is a valuable method for locating liver and peritoneum metastases. In our series, ultrasound diagnostics were only carried out in patients with abdominal tumors or pain at the beginning of the diagnostic process, and was useful only to confirm the suspicion of malignancy based on the presence of metastases.

Computer tomography is also limited in the diagnosis of gastric GIST due to a lack of any characteristic features of GISTs [26]. The computer tomography image of gastric GIST is very similar to other tumors of the gastrointestinal wall (e.g. sarcomas, carcinoid tumors etc.) [26]. Moreover, in the case of large lesions, the point of origin is difficult to ascertain due to invasions of surrounding organs [26].

In the present study, no imaging method facilitated a correct diagnosis of GIST. Neither CT scans nor ultrasound scans showed the point of origin of large tumors and the results of these imaging methods were also uncharacteristic of small lesions.

It seems that the best diagnostic method for gastric GIST is endoscopy. However, the lesion may be impossible to detect endoscopically due to its submucosal location [13]. A typical endoscopic image of gastric GIST registers a submucosal tumor or wall elevation as possessing a normal mucosal surface. An ulceration on the surface of a lesion is observed during endoscopy in some cases of gastric GIST. Ulceration of the GIST surface usually contains a normal mucous cell [11]. Therefore, a tissue sample collected from the ulceration cannot usually provide a definite histopathological diagnosis.

Due to the submucosal location of the GIST lesion, a preoperative histopathological diagnosis of gastric GIST based on endoscopy with tissue sample collection is unclear in 15–50% of GIST cases [11, 13]. Fine needle aspiration biopsy guided with ultrasonography is characterized by low accuracy [13].

Fine needle aspiration biopsy is a method intended for palpable tumors whose origin and character is difficult to establish; these tumors usually present a solid-cystic architecture. The main disadvantage of GIST biopsy is the possibility of the sample being collected from the non-diagnostic area of the cystic part of the tumor. In all group 1 patients, the GIST diagnosis was given based on endoscopy with tissue sample collection.

The Ki-67 protein is a protein involved in cell proliferation. Neto et al. demonstrate a strong statistical correlation between Ki-67, histological grade, mitotic index and presence of necrosis [1]. The authors also suggest a statistically significant relationship between Ki-67 expression and poor survival rate. The present study shows comparable results. A significant difference was seen in Ki-67 expression between both study groups. A significantly lower survival rate was seen in patients with difficulties in gastric GIST diagnosis (group 2), as well as a correlation between Ki-67 expression, mitotic index and histological grade.

In the present study, survival rate varied between the two groups. The survival rate was significantly lower in patients with difficulties in GIST tumor diagnosis (66% vs. 10%). Recently published studies report a survival rate of 70–80% [28, 29].

Only the survival rate of group 2 patients differed dramatically from published data.

Mitotic count and size are the most recognized prognostic factors for GIST tumors [30]. The mitotic count and size were significantly greater in group 2 than in group 1, as well as in data from recent publications. Besides other factors such as cellular atypia, a high histological grade and the presence of metastases determined high proliferation activity and low survival rate in group 2 patients.

This study is limited by being retrospective and the small number of patients in the subgroups. However, our findings suggest that GIST tumors with a difficult diagnosis are diagnosed in a late stage of the disease. The more advanced stage of the tumor probably results from faster tumor growth due to higher proliferation activity.

GIST tumors with a difficult diagnosis are characterized by a lower survival rate due to the later stage of the disease at the time of diagnosis.

Acknowledgements. The authors thank Ed Lowczowski, language consultant.

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Conflict of interest: None declared

Received: 16.01.2013
Revised: 28.01.2014
Accepted: 23.07.2014