RESEARCH ARTICLE

Prognostic Factors for Large Symptomatic Gists: a Pragmatic Study of Experiences From a University Hospital Over 10 Years

Supatcha Prasertcharoensuk[1]*, Punnapud Thanapongpornthana[2], Vajarabhongsa Bhudhisawasdi[1], Ake Pugkhem[1], Kriangsak Jenwitheesuk[1], Aumkhae Sookprasert[3], Chawalit Pairojkul[4]

Abstract

Background: Gastrointestinal stromal tumors (GISTs), which are mesenchymal neoplasms in the gastrointestinal (GI) tract account for 0.2% of all GI tumors. Several factors have been reported (mostly from studies conducted in Western countries) to be associated with survival in GISTs cases such as tumor site, staging, and tumor size. We conducted a pragmatic study, looking at a 10-year period, aimed at understanding the prognostic factors related to GISTs in a university hospital. The study population consisted of patients with large symptomatic GISTs. **Methods:** This was a retrospective study conducted at the Department of Surgery in the Khon Kaen University Hospital (Thailand). All patients diagnosed with GISTs that were treated between 2006 and 2015 were consecutively enrolled. The diagnosis of GISTs was made by examining the pathological section and immunohistochemistry results. The outcome of this study was the rate of survival after surgical treatment. Prognostic factors were determined using Cox regression analysis. **Results:** There were 124 GISTs patients treated at the university hospital during the 10-year period of the study. The median age of all patients was 54 years (range 24-83 years). Of those, 119 (95.9%) were symptomatic. Rectosigmoid GISTs accounted for 20.2% of all tumors. The median tumor size was 8 cm. A total of 68 patients (54.8%) died. The median survival time for all patients was 7.18 years (1st -3rd quartile range 6.48-7.89). There were three significant factors associated with death including male gender, liver metastasis, and peritoneal metastasis. **Conclusion:** Male gender, liver metastasis, and peritoneal metastasis were prognostic factors for large symptomatic GISTs.

Keywords: Male- rectum- gastrointestinal stromal tumors

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Introduction

Gastrointestinal stromal tumors (GISTs), which are mesenchymal neoplasms in the gastrointestinal (GI) tract (Miettinen and Lasota, 2011), accounted for 0.2% of all GI tumors. (Blay et al., 2005) In the past, GISTs had often been misclassified as smooth muscle cell tumors or tumors originating in the nerve sheath due to lack of specific markers and there having been few studies conducted (Fletcher et al., 2002; Chan et al., 2006; Wang et al., 2001). In 1983, Mazur and Clark first described a heterogenous group of GI non-epithelial neoplasms as GISTs. In 1988, Hirota et al. also reported that GISTs contain an activating c-kit mutation (Mazur and Clark, 1983; Hirota et al., 1998). Currently, GISTs are believed to originate from the interstitial cells of Cajal throughout the GI tract which generate electrical pacemaker activity for GI motility (Hirota et al., 1998).

Gastrointestinal stromal tumors are associated with the activation of mutations in KIT or platelet-derived growth factor receptor alpha (PDGFRα) genes. Gastrointestinal stromal tumors that are not associated with these genes are classified as wild-type GISTs and account for 10-15% of these tumors (Sanders et al., 2006). Gastrointestinal stromal tumors can originate in any area in the GI tract, but most commonly originate in the stomach (50-60%) (Heinrich et al., 2003; Rubin et al., 2007). Most GISTs patients present with various GI symptoms such as nausea, vomiting, dyspepsia (Nilsson et al., 2005; van der Zwan and DeMatteo, 2005). The liver is the most common metastatic site (Iqbal et al., 2015; Vassos et al., 2015).

The main treatment for GISTs is surgical resection, but is not routinely performed (DeMatteo, 2002; Demetri et al., 2007). Imatinib mesylate or Gleevec ®, an oral inhibitor of KIT and platelet-derived growth factor receptors, is also approved for the treatment of metastatic GISTs (Dagher et al., 2002). The overall five-year survival rate in GISTs cases is approximately 50%. Studies (mostly from Western countries) have reported several factors to be associated with survival in cases of GISTs such as tumor

*[1]Department of Surgery, [3]Division of Oncology, Department of Internal Medicine, [4]Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, [2]Surgical Unit, Buriram Hospital, Buriram Thailand. *For Correspondence: supatcha.p@gmail.com*

site, staging, and tumor size (Hassan et al., 2008; Del Rio et al., 2016; Cao et al., 2010). We conducted a 10-year pragmatic study aimed at understanding the prognostic factors related to GISTs in an Asian university hospital.

Material and methods

This was a retrospective study conducted at the Department of Surgery in Khon Kaen University Hospital (Thailand). All patients diagnosed as having GISTs who were treated between 2006 and 2015 were consecutively enrolled. The diagnosis of GISTs was made by examination of the pathological section and immunohistochemistry results.

Baseline clinical data at the time of diagnosis were recorded including age, gender, symptoms, modified NIH classification (Belfiori et al., 2015), treatment, laboratory results, and treatment outcomes. The treatment protocol used in our hospital is surgery and/or imatinib mesylate. The imatinib mesylate is indicated in metastatic patients, in patients with unresectable primary tumors prior to subsequent surgical resection (neoadjuvant therapy), or in cases of large tumors (as determined by the individual surgeon).

Statistical analyses

Patients were categorized as either "died" or "survived". Clinical factors were compared between the two groups using descriptive statistics. The Kaplan-Meier method and Cox regression analysis were used to execute the survival-related outcomes. The average survival rate for each year was calculated using the Kaplan-Meier method, while prognostic factors were executed using Cox regression analysis. The Cox regression analysis outcomes were determined according to date of pathological diagnosis to date of death or last follow up for each patient. All analysis was performed using STATA software (College Station, Texas, USA) version 14.0.

Results

There were 124 GISTs patients treated at the university hospital during the 10-year period of the study. The median age of all patients was 54 years (range 24-83 years). Of those, 66 patients were male (53.2%), only 5 patients (4.1%) were asymptomatic, and 57 patients (46.0%) had metastatic lesions at the time of presentation, mostly in the liver (86.0%), as shown in Table 1. The top three most common primary sites of GISTs were the stomach, the small intestine, and the rectosigmoid (Table 1). The median tumor size was 8 cm (range 1.5-30.0 cm), while the most common histopathological cell type was spindle (70.2%), followed by epithelioid (14.9%) and mixed (14.9%).

Table 1. Clinical Factors of Patients with Gastrointestinal Stromal Tumors (N=124) Categorized by Death Outcome

Factors	Survived n = 56	Died n = 68	p value
Age, years	53 (28-79)	56 (24-83)	0.703
Male sex	30 (53.57)	36 (52.94)	0.999
Presenting symptom			0.043
Asymptomatic	3 (5.36)	2 (2.99)	
Gastrointestinal bleeding	13 (23.21)	13 (19.40)	
Abdominal mass	11 (19.64)	30 (44.78)	
Others	23 (41.07)	18 (26.87)	
Organ involvement			0.73
Stomach	20 (36.36)	19 (28.36)	
Small intestine	18 (32.73)	18 (26.87)	
Rectosigmoid	8 (14.55)	17 (25.37)	
Size, cm	8 (1.5-21)	8 (5-30)	0.395
Modified NIH score	4 (2-4)	4 (2-4)	0.71
Metastasis			<0.001
No	43 (76.79)	24 (35.82)	
Liver	13 (23.21)	36 (53.73)	
Peritoneal	0	2 (2.99)	
Treatment with imatinib mesylate			0.018
No	20 (35.71)	16 (23.88)	
Neoadjuvant prior to surgery	9 (16.07)	10 (14.93)	
Metastasis	13 (23.21)	33 (49.25)	
Large tumor mass	14 (25.45)	8 (11.94)	
Cell type, spindle	14 (77.78)	19 (65.52)	0.72
CD117	40 (90.91)	53 (89.83)	0.999

Data is presented as numbers (percentage) or median (range); the total numbers of patients may not equal to 56 in the "survived" group and 68 in the "died" group due to missing data; NIH, the National Institutes of Health (NIH) consensus classification system; CD117, tyrosine-protein kinase Kit

Table 2. Survival Rate in Years in Patients with Gastrointestinal Stromal Tumors (N=124)

Years	Survival rate (%)	95% confidence interval
1-	87	79-91
3-	75	67-82
5-	62	52-70
7-	54	44-62
9-	39	29-49

Sixty-eight of the patients enrolled in the study (54.8%) died. There were three factors that differed significantly between those who survived and those who died, including presenting symptoms, metastasis, and treatment with imatinib mesylate (Table 1). A higher proportion of the patients who died presented with abdominal mass (44.78% vs 19.64%), liver metastasis (53.73% vs 23.21%), and underwent imatinib mesylate treatment due to evidence of metastasis (49.25% vs 23.21%) than those who survived.

The median survival time for all patients was 7.18 years (1st -3rd quartile range 6.48-7.89). The five-year survival rate was 62% (95% confidence interval of 52-70), as shown in Table 2. There were three significant factors associated with death according to univariate Cox proportional hazards analysis including epithelioid cell type, liver metastasis, and peritoneal metastasis. After multivariate Cox proportional hazards analysis, only male gender, liver metastasis, and peritoneal metastasis were independently associated with death (Table 3).

Discussion

The study population had different characteristics from those in previous studies (Heinrich et al., 2003; Rubin et al., 2007). This study found double the amount of rectal GISTs (20.2%) found in a similar US study (10%) (Rubin et al., 2007) and 4 times the amount found in a study from China (5.0%) (Cao et al., 2010). Additionally, almost 100% of the patients in this study had GI symptoms (96%), while only 70% of patients presented with symptoms in other studies (Nilsson et al., 2005; van der Zwan and DeMatteo, 2005). These findings may be explained by tumor size. In cases of symptomatic GISTs, the median tumor size found was 8.9 cm as Nilsson (2005) reported in his previous work, which was comparable to the median tumor size found in all patients in this study (8 cm). The median tumor size in incidental patients and autopsy cases in that study were 2.7 and 3.4 cm, respectively (Nilsson et al., 2005). In other words, a greater proportion of the study population in this study had large or symptomatic GISTs.

The three independent prognostic factors for GISTs death in this study were male gender, liver metastasis, and peritoneal metastasis (Table 3). Male patients had a 66% increased risk for mortality. A previous study also showed that male patients had a lower average five-year survival rate than female patients (92.3% vs 100%; p value 0.033) if they were under 50 years old (Kramer et al., 2015). The difference in survival rates between male and female patients was not significant if they were over 50 (78.5% vs 83.2%).

Unlike previous studies, we did not find the site of the GISTs to be significantly related to mortality or survival. Previous studies have found that patients with GISTs in the small intestine may have higher mortality rates, with a hazard ratio of 2.6 (Hassan et al., 2008). In this study, rectal GISTs were not independently associated with mortality even though they were found in high proportions compared with previous studies, as mentioned earlier (Table 3). The two strong predictors for death in this study were liver and peritoneal metastasis (Table 3). These results were not surprising, as they were similar to those of previous studies (Hassan et al., 2008; Cao et al., 2010). Higher NIH classification or advanced disease increased the risk of death by 3.378 times (Cao et al., 2010). What was new in this study was that it showed that presence of peritoneal metastasis was strongly associated with the risk of death (6.56 times higher).

The strength of this study was its sample size. The study population was comparable to those of other previous studies (Nilsson et al., 2005; Hassan et al., 2008; Del Rio et al., 2016; Cao et al., 2010). The fact that it was a pragmatic study may be either an advantage or disadvantage. While clinical practice research may reflect real-life outcomes, some factors cannot be controlled, such as treatment options or characteristics of patients. Due to the retrospective study design, some factors are missing. These results may apply only in cases of patients with large tumors or who have symptomatic GISTs. Further studies may be needed to confirm the results of this study.

Male gender, liver metastasis, and peritoneal metastasis were prognostic factors for symptomatic, large tumor GISTs.

Statement of Author Contribution

The authors declare, they have no competing interests as defined by the Asian Pacific Journal of Cancer

Table 3. Factors Associated with Death in Patients with Gastrointestinal Stromal Tumors according to Cox Regression Analysis (N=124)

Factors	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio (95% confidence interval)
Male sex	1.51 (0.92-2.46)	1.66 (1.01-2.74)
Epithelioid cell type	2.94 (1.01-8.52)	-
CD117	1.47 (0.61-3.50)	-
Rectum	1.19 (0.61-2.30)	-
Liver metastasis	2.09 (1.24-3.51)	2.11 (1.26-3.55)
Peritoneal metastasis	5.05 (1.16-21.87)	6.56 (1.47-29.23)

Prevention.

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