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A cohort study of prognostic factors associated with recurrence or metastasis of gastrointestinal stromal tumor (GIST) of stomach

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ABSTRACT

Background: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. The major risk factors of recurrence and metastasis are mitotic index and tumor size. This study investigates the risk of recurrence and metastasis in solely gastric GIST. The primary outcome is to evaluate risk of recurrence and metastasis. The secondary outcome is to analyse survival rates of patients who have recurrence and metastasis after curative resection.

Method: A cohort of patients who underwent curative resection of gastric GIST between January 2006 to December 2016 was reviewed. The diagnosis was confirmed with positive CD34, DOG1 or KIT (CD117) immunohistochemistry. Risk factors of recurrence and metastasis were analyzed.

Results: Sixty-eight patients who received curative resection and diagnosed as gastric GIST were included in this study. Twenty (29.41%) had recurrence or metastasis. The median follow up time was 31.95 months. The mostcommon type of surgery was partial gastric resection. There were statistically-significant differences between mitotic index 6 HPF or 6 HPF in tumor size 0-5 cm, 5-10 cm and 10 cm and the risk of recurrence or metastasis (p-value 0.036). In tumors sized 6-10 cm, patients with mitotic index 6 HPF had longer survival than patients with mitotic index 6 HPF (p-value 0.0147).

Conclusion: The factor that determines the outcome of recurrence or metastasis in solely gastric GIST is high mitotic index count. Patients who have abdominal pain may be suspected as advanced disease. The type of operation and tumor size are not associated with recurrence or metastasis.

1. Introduction

Gastrointestinal stromal tumor (GIST) is a relatively rare tumor [1]. GISTs are the most common mesenchymal tumors of the digestive tract. They account for the majority of intramural tumors and can vary widely in appearance, from small intraluminal lesions to exophytic masses that protrude into the peritoneal cavity, commonly with areas of hemorrhage or necrosis. GISTs originate within the smooth muscle layer in the wall of the tubular gastrointestinal tract and grow mostly toward the serosa, far less often toward the mucosa.

The cell origin of GIST arises from interstitial cell of Cajal and is characterized by mutation of KIT and platelet derived growth factor receptor (PDGFR) [2]. The standard curative treatment of GIST is complete surgical resection with negative margin from the tumor. The evaluation risk s of recurrence and metastasis depend on various factors including tumor location, mitotic rate, tumor size, and tumor rupture. Fletcher et al. classified the risk of recurrence or metastasis of surgically resected primary GIST as very low, low, intermediate, and high risk by using the tumor size and mitotic count [3]. Miettinen and Lasota developed a method to predic t the risk of recurrence and metastasis which included the tumor location i.e. stomach, jejunum and ileum, duodenum, and rectum together with the tumor size and mitotic rate [4]. The other characteristic s for high -risk of recurrence are high cellularity, inva sion of adjacent organs, and tumor rupture.

Gastrointestinal stromal tumors (GISTs) are rare life threatening forms of cancer representing 0.1–3% of all the GI malignancies. When one compares between gastric GIST and GIST from other locations, i.e. esophagus, small intestine, colon, rectum or extra-gastrointestinal GIST (EGIST), gastric GIST have a better prognosis. The recurrence free survival of gastric GIST is longer than that of GIST from other organs

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with the same size or mitotic rate [2,5,6]. Because GIST are heterogeneous of clinical and morphology which are difficult to predict the prognosis of the disease [7]. Few studies have focused on the specific risks of solely gastric GIST and some reports have shown the size not correlated the risk of recurrence [8]. Therefore, the primary aim of this study was to evaluate the risk of recurrence and metastasis of solely gastric GIST receiving curative resection. The secondary aim was to analyse the survival rate of solely gastric GIST patients who have recurrence and metastasis.

2. Materials and methods

A retrospective cohort of all patients aged 18 years or older who presented with gastric GIST and underwent curative surgical resection from January 2006 to December 2016 was reviewed. Ethical issues were approved by Faculty of Medicine Ramathibodi Hospial Ethics Committee and registered in Research Registry. The patients who had involvement of other organs or metastasis before curative surgery were.

excluded. Curative surgical resection was defined as total resection of all tissue s invaded by the tumor with a free margin, including lymphatic resection if nessesary. The tumor specimen s were diagnosed by a pathologist and confirmed by immunohistochemistry with one of the followings: CD34, DOG1 or KIT (CD117). The patients who had recurrence or metastasis at the time of follow up were identified. The diagnosis tools for detection of recurrence or metastasis were esophagogastroduodenoscopy (EGD) or imaging studies include ultrasonography, computer tomography (CT), or magnetic resonance imaging (MRI). Age, gender, chief complaint s, EGD finding s, imaging finding s, tissue dianosis before surgery, intraoperative finding s, tissue immunohistochemistry after complete surg ical resection, adjuvant treatment, and the time of recurrence or metastasis were analysed.

2.1. Statistical analysis

The data were analysed by using STATA version 14. The logistic regression was used to evaluate the risk of recurrence or metastasis and reported 95% CI (confidence interval) of OR (odds ratio). The Pearson Chi Square was used to compare and categorize between size and mitotic index for risk of recurrence and metastasis. The p-value < 0.05 was considered statistically significant.

3. Results

Between January 1, 2006 and December 31, 2016, 68 patients were diagnosed as solely gastric GIST and received curative resection. Forty-eight patients had no recurrence or metastases, whereas 20 patients (29.41%) had recurrence or metastasis. The median follow up time was 31.95 months (IQR 14.6–52.7). The patients' characteristics are shown in Table 1. Diabetes mellitus was significantly associated with increased risk of recurrence or metastasis ($p = 0.025$). However, after multivariated analysis, no underlying disease was found to be associated with increased risk of recurrence or metastasis. Like diabetes mellitus, abdominal pain was the only presenting symptom which was significantly associated with recurrence or metastasis ($p = 0.022$); however, the result was not different in multivariated analysis.

The location of tumors was classified as proximal, middle, and distal part of the stomach according to Japanese classification of Gastric Carcinoma [9]. The most-common tumor location in all patients was proximal, followed by middle, and lower part, respectively. No association between location of tumor and recurrence or metastasis was found ($p = 0.666$). There was no statistical significance between the types of the operation and recurrence or metastasis ($p = 0.965$). Rupture of tumor during operation was found in 3 cases in the group of patients without recurrence or metastasis and one case in.

3.1. Group of patients with recurrence or metastasis. `

The tumor size, mitotic index and the correlation of recurrence and metastasis are shown in Tables 2–4. There is a statistically significant association between mitotic index > 6 HPF (95% CI 1.802–24.653, $p = 0.004$) and risk of recurrence or metastasis (Table 3). There is a statistically significant difference between mitotic index ≤6 HPF or > 6 HPF in tumor size 0–5 cm, > 5–10 cm and > 10 cm and the risk of recurrence or metastasis (p-value 0.036) (Table 4).

In patients who had recurrence or metastasis (20 patients), 7 (35%) had liver metastasis, 1 (5%) had peritoneal metastasis, 1 (5%) had lung and liver metastasis and 11 (55%) had tumor recurrence. Most patients received systemic treatment following the standard protocol, except for some patients who did not receive systemic treatment due to personal financial constraints. Seventeen out of twenty patients in the recurrence or metastasis group received Imatinib. In survival analysis, the size of tumor did not affect overall survival in either group of mitotic indexes less or more than 6. However, the mitotic index less than or equal to 6/HPF and more than 6/HPF had a statistically significant difference in each size of tumor (range 0–5 cm, > 5–10 cm and > 10 cm).

In the tumor size 0–5 cm, patients with mitotic index ≤6 HPF had longer survival than patients with mitotic index > 6 HPF, but does not show statistical significance (p-value 0.0827). In the tumor size 6–10 cm, the patients with mitotic index ≤6 HPF had longer survival than patients with mitotic index > 6 HPF (p-value 0.0147). For tumor size > 10 cm, there is no statistical difference between mitotic index ≤6 HPF and > 6 HPF (p-value 0.4254).

The median follow up time was 31.5 months (range 0.4–330 months). The median follow up time for patients with liver metastasis, liver and lung metastasis, and peritoneal metastasis were 24.19, 11.53 and 10.52 months, respectively. The survival analysis was performed for patients with recurrence or metastasis (Fig. 1). The mortality rate for patients who had recurrence or metastasis and non-recurrence or non-metastasis patients were 0.444/100/month (5.33 patients/year) and 0.051/100/month (0.61 patients/year), respectively.

4. Discussion

In this study, we included 68 patients who were diagnosed with gastric GIST. At the initial presentation, all patients had no metastasis and underwent curative resection surgery, and some patients.

received systemic treatment following standard protocol. We found that tumor size between patients with and without recurrent or metastasis group does not show a statistical significance (p-value 0.612). Only high mitotic index shows a statistical significance (p-value 0.004) that could predict the high risk of recurrence or metastasis in these patients.

For patients in the recurrence or metastasis group in this study, the correlation between size and mitotic index in all patients did not affect the recurrence or metastasis. Independent to mitotic count, the data do not show a statistical significance in all ranges of tumor. Regarding the mitotic index, a statistical significance is found in mitotic index > 6 HPF (95% CI. 1.802–24.653, p-value 0.004). The correlation between tumor size and mitotic index shows a statistical significance (p-value 0.036) in mitotic count more than 6 HPF by independent to size of tumor which like some report has shown the size not correlated with the risk of recurrence [8]. Finally, these data were interpreted that only mitotic index more than 6 HPF affected recurrence or metastasis and does not depend on tumor size.

After follow up time, (median follow up time was 31.5 months), we found 20 patients had recurrence or metastasis. In the patients with recurrence and metastasis, the total mean age was 63.25 years and 59.25 years in patients with and without recurrent or metastasis group, respectively. This is similar to several other studies which found the mean age more than 50 years [10].

In these data, we found that the most-common underlying disease