

Original Article

## The Clinicopathologic Features and Outcome of Patients with Gastrointestinal Stromal Tumors in Colorectal Region

Hsueh-Li Yang  
Shih-Ching Chang  
Yu an-Tzu Lan  
Huann-Sheng Wang  
Shung-Haur Yang  
Jeng-Kae Jiang  
Wei-Shone Chen  
Tzu-Chen Lin  
Jen-Kou Lin

Division of Colorectal Surgery, Department  
of Surgery, Taipei Veterans General  
Hospital, Taiwan

### Key Words

GIST;  
Colorectal cancer

**Background.** Gastrointestinal stromal tumor (GIST), originated from c-kit mutation, is a rare tumor in colorectal region. This study was to describe the clinicopathologic features and outcome of patients with colorectal GIST.

**Methods.** We prospectively recorded the clinical data of colorectal tumors receiving operations in Taipei-Veterans General Hospital since 1997. The patients with the diagnosis of GIST were reviewed for the clinical courses and pathological results. The diagnosis of GIST was confirmed by positive staining of CD117 in immunohistochemistry.

**Results.** From Dec. 1997 to Oct. 2008, 19 of the 4205 patients (0.44%) were diagnosed to have GIST. The mean age was  $61.3 \pm 16.2$  year-old (range: 23-81 year-old). Fourteen (74%) were male. Fourteen (74%) tumors located at rectum. The mean diameter of tumor was  $4.0 \pm 3.3$  cm. The largest size of the tumor was  $13 \times 7 \times 6$  cm. Eleven tumors showed high grade mitosis. Fifteen patients received radical resection. Nine patients received imatinib treatment for high grade mitosis, large tumor size ( $> 5$  cm in diameter) and intraabdominal seeding. The average follow-up period was  $40.2 \pm 29.8$  months (range: 3-111 months). Eleven patients had high mitosis ( $\geq 5/50$  HPF), 7 of them had recurrent disease in 56 months (median =  $29.9 \pm 21.7$  months). For patients with low mitosis tumor, survival rate was 87.5%, better than those with high mitosis (54.6%). High risk patients had higher risk of tumor recurrence (66.7%).

**Conclusion.** Patients with GIST who had large tumor size (tumor size  $> 5$  cm, recurrent rate 100%) or high mitosis (mitosis  $\geq 5/50$  HPF, recurrent rate 63.5%) in pathological analysis had higher incidence of tumor recurrence, even after radical surgical resection.

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**G**astrointestinal Stromal Tumors (GISTs) are the most common mesenchymal neoplasm of the digestive tract. About 1%~3% of all GI cancers is GIST. It arises from interstitial cells of Cajal, a muscle

like nerve cells that coordinate the autonomic movements of the GI tract.<sup>1-3</sup> CD117 (c-kit) mutation can be detected in around 90% of GIST. Besides CD117, CD34 mutation (60-70%) and platelet-derived growth

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Correspondence to: Dr. Shih-Ching Chang, Division of Colorectal Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Beitou District, Taipei 11217, Taiwan. Tel: +886-2-2871-2121; Fax: +886-2-2873-2131; E-mail: yeaby1128@yahoo.com.tw

factor receptor, alpha polypeptide mutation (PDGFRA, 5-10%) also present in the GIST.<sup>2,4</sup> KIT protein (CD117) is a transmembrane type-III tyrosine-kinase receptor.<sup>1,2</sup> It also present in mast cells, hematopoietic stem cells, melanocytes, germ cells, mammary ductal epithelia, angiosarcomas, melanomas, and seminomas, etc.<sup>4-6</sup> There are three categories of morphology of GIST: Epithelioid type (20-30%); spindle cell type (70-80%); and mixed type (10%) (Fig. 1).<sup>1,7</sup> GISTs are often discovered incidentally by computed tomography (CT) or endoscopy. CT and Positron Emission Tomography (PET) are both useful for pre-op staging. CT shows greater anatomic details than PET whereas PET can reveal small metastases. The Canadian Advisory Committee on Gastrointestinal Stromal Tumors recommended GIST patients should follow CT every 3-6 months for a minimum of 5 years even receiving complete tumor resection.<sup>2</sup>

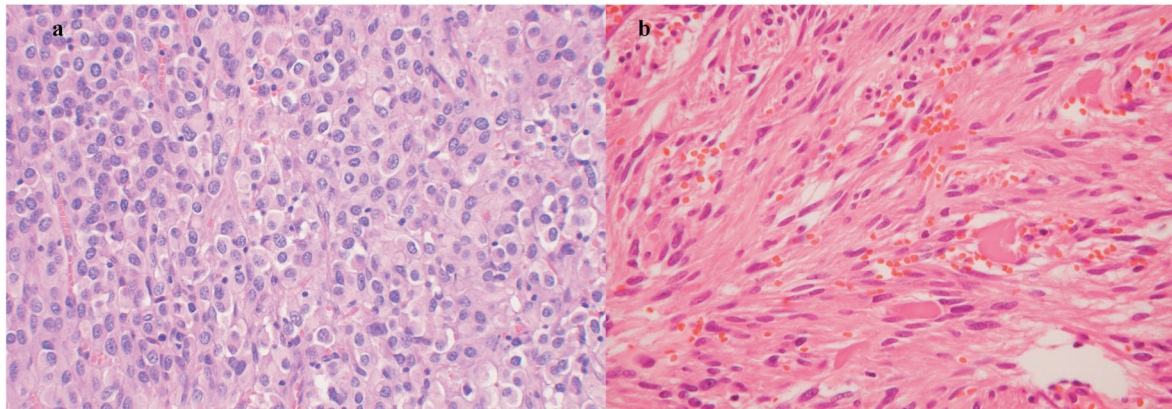
For localized disease, complete gross resection is

the gold standard of treatment. Resection should avoid tumor rupture because high risk of intra-abdominal dissemination would occur after tumor rupture. For advanced disease, it responds poorly to conventional cytotoxic chemotherapy and radiation therapy. For such unresectable or metastatic GIST, imatinib (gleevec, glivac), a tyrosine kinase inhibitor is the treatment of the choice.<sup>2,8,9</sup> According to the Fletcher's criteria<sup>3</sup>, GIST with large tumor size (> 5 cm) and/or higher mitosis ( $\geq 5/50$  HPF) will have higher metastatic potential.

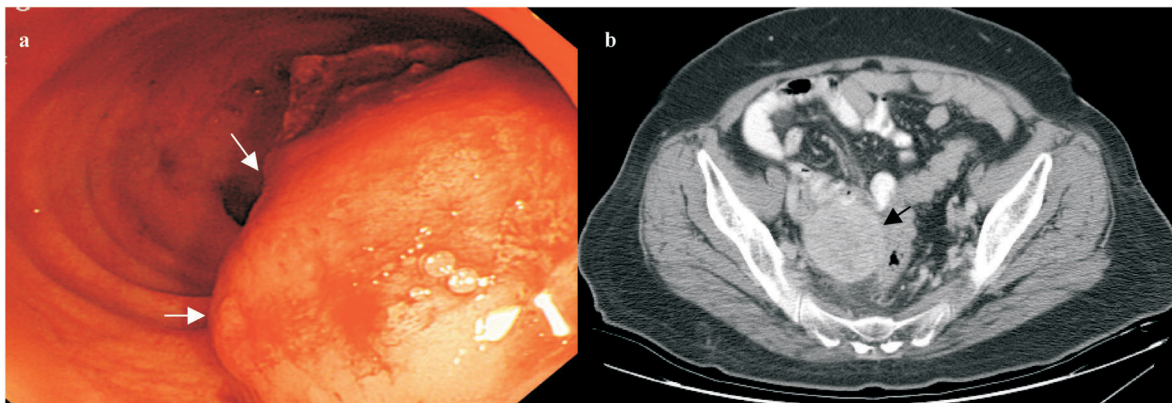
Our study was to describe the clinicopathologic features and outcomes of patients with colorectal GIST in Taipei-Veteran General Hospital.

## Patients and Methods

We prospectively recorded the clinical data of



**Fig. 1.** (a) Epithelioid type (20-30%); (b) spindle cell type (70-80%).<sup>8</sup>



**Fig. 2.** (a) GIST found by colonoscopy; (b) CT scan of sigmoid colonic GIST.

colorectal tumors receiving operations in Taipei-Veterans General Hospital from Dec. 1997 to Oct. 2008. 19 of the 4205 patients with colorectal tumors (0.44%) were diagnosed to have GIST. The patients with the diagnosis of GIST were reviewed for the clinical courses and pathological results. Most patients received radical treatment. Only patients with low rectal tumor ( $\leq 5$  cm from anal verge) and small tumor size ( $\leq 3$  cm) received local treatment for preserving the anus while curative resection was done. The tumor recurrence was defined as recurrent tumor or distant metastasis found by follow-up image or colonoscopy. The patients were followed-up after curative resection with CT and colonoscopy.

According to the Fletcher criteria<sup>3</sup>, GIST can be divided into very low risk (tumor size  $< 2$  cm and mitotic counts  $< 5/50$  HPF), low risk (tumor size 2-5 cm and mitotic counts  $< 5/50$  HPF), intermediate risk (tumor size  $< 5$  cm and mitotic counts 6-10/50 HPF or tumor size 5-10 cm and mitotic counts  $< 5/50$  HPF), and high risk (tumor size  $> 5$  cm and mitotic counts  $> 5/50$  HPF or tumor size  $> 10$  cm with any mitotic rate or mitotic counts  $> 10/50$  HPF with any tumor size). The followed up interval of the GIST was different to the principle of colorectal adenocarcinoma. The follow up interval and period were different according to the GIST risk. Low risk GISTs had a follow-up CT at 12 months. Intermediate risk GISTs had a follow-up CT at 9 months, then annual scan thereafter for 4 years. High risk GISTs had a CT every 6 months for 3 years, followed by annual CT for a further 2 years. Follow-up colonoscopy was done annually after curative resection. The diagnosis of GIST was confirmed by positive staining of CD117 in immunohistochemistry. Tumor mitosis was separated to high ( $\geq 5/50$  HPF) and low mitosis ( $< 5/50$  HPF).

### Statistical analysis

Descriptive statistics were summarized as means, standard deviations, and as frequencies and ranges for the survival difference using the SPSS 16.0 statistical software. When inference testing was completed, results with a *p* value less than or equal to 0.05 were considered statistically significant.

## Results

Totally 19 patients were diagnosed as GIST by positive immunohistochemical staining of KIT protein (CD117). The demographic data were showed in Table 1. The mean age was  $61.3 \pm 16.2$  year-old (range: 23-81 year-old). Most patients had symptoms of bowel habit change ( $n = 10, 52.6\%$ ). Three patients complained about rectal bleeding while defecation. One patient had the symptoms of abdominal pain. The others were accidental finding via colonoscopy. There were 5 colonic GISTs and 14 rectal GISTs. The mean tumor size was  $4.27 \pm 3.19$  cm. The follow-up periods were  $40.2 \pm 29.8$  months (range: 3-111 months). There were 15 patients receiving radical resection, and 7 (46%) patients had recurrence in the median of  $25.7 \pm 18.4$  months. Among these patients with radical resection, one had R1 resection and had local recurrence in 27 months, and one had R2 resection and had distant metastasis at the time of the surgery. Four patients received local resection and all of them had R0 resection. Among these patients with local treatment, only one had recurrence 56 months after surgery (Fig. 3).

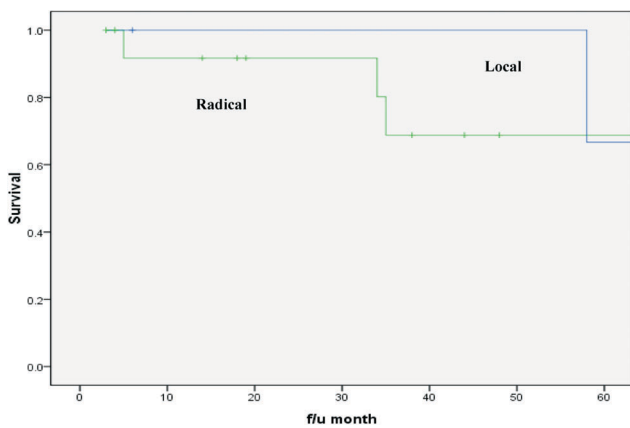
The median survival of R0 resection, including radical and local resections, was  $40.5 \pm 30.6$  months. Only one patient had R1 resection and had received further operation, the survival period of this patient was 44 months. One patient had distant metastasis at the time of operation, the survival period of this patient was 5 months.

According to Fletcher criteria, tumor size and mitosis are most important predictive factors of metastatic potentials. As our results shown in Table 2, five patients had large tumor size ( $> 5$  cm), and all of them had recurrent disease in 27 months (median =  $16 \pm 9.1$  months). Patients with large tumor size had poor prognosis (Fig. 4). 11 patients had high tumor mitosis ( $\geq 5/50$  HPF), 7 of them had recurrent disease in 56 months (median =  $29.9 \pm 21.7$  months). Survival was better in low mitosis group (Fig. 5). In Table 2, high risk patients had higher risk of tumor recurrence (66.7%). In Fig. 6, low risk patients (100%) had higher disease free survival than high risk patients (33.3%).

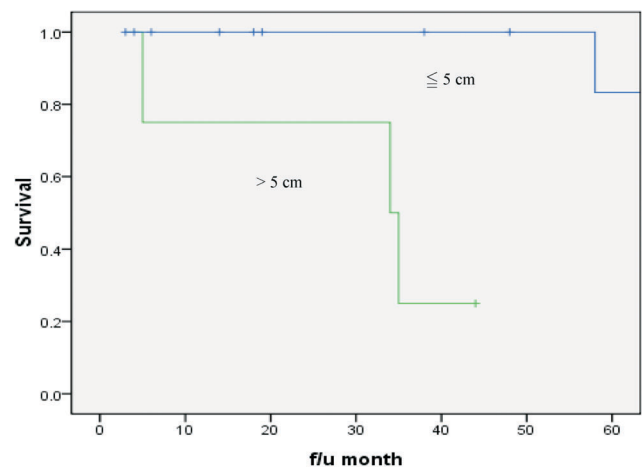
Most of the patients in our series had spindle cell

**Table 1. The demographic presentation of 19 GIST patients**

		n	%	Recurrence %	<i>p</i>
Gender	Male	14	74		
	Female	5	26		
Location	Rectum	14	74	5 (36%)	
	Colon	5	26	3 (60%)	
Tumor size	≤ 5 cm	14	74	3 (21.4%)	0.001
	> 5 cm	5	26	5 (100%)	
Mitosis	< 5 /50 HPF	8	42	1 (12.5%)	0.030
	≥ 5/50 HPF	11	58	7 (63.5%)	
Treatment	Radical:	15	79	7 (46%)	0.344
	LAR (n = 10)				
	AR (n = 2)				
	L't hemicolectomy (n = 2) R't hemicolectomy (n = 1)				
Transanal (local)		4	21	1 (25%)	
Margin	R0	Radical	13	86.6	5 (38.5%)
		Local	4	100	1 (25%)
	R1	Radical	1	6.7	1 (100%)
		Local	0	0	0
	R2	Radical	1	6.7	1 (100%)
		Local	0	0	0
Histology	Epitheloid	0	0	0	
	Spindle	16	84.2	7 (43.8%)	
	Mixed	3	15.8	1 (33.3%)	
Imatinib	9 patients (high grade and/or recurrence)				



**Fig. 3.** Survival difference according to type of the surgery, *p* = 0.344.

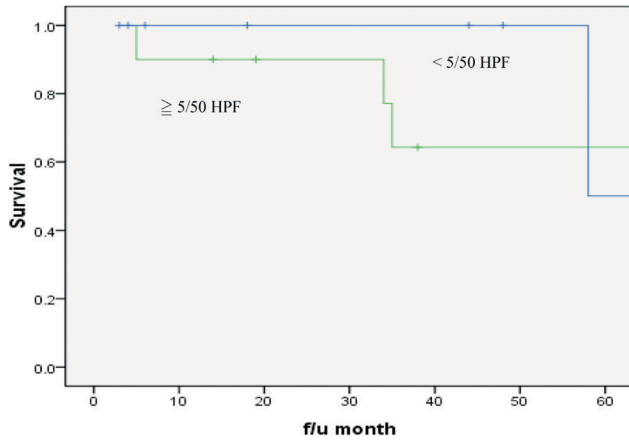


**Fig. 4.** Survival difference according to the tumor size.

type in morphology (n = 16, 84.2%). Only three patients had mixed cell type and no patients has epitheloid type. The recurrent rate was 43.8 % in spindle cell type and 33.3% in mixed cell type. The median

survival of the patients with spindle cell type of the GIST was 40.5 ± 31.4 months and with mixed cell type was 19 ± 16 months.

In all of the 19 patients, three patients had local re-



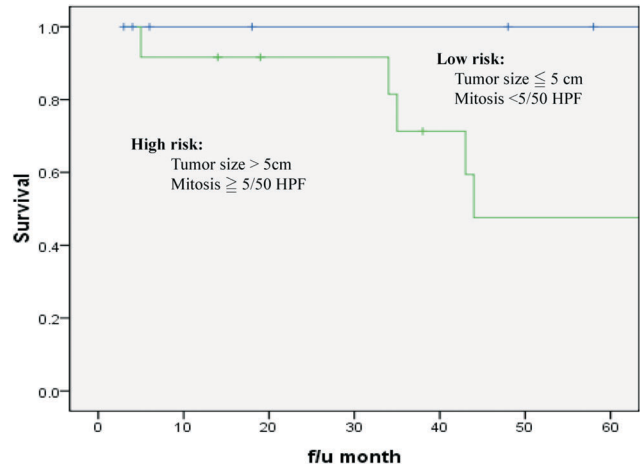
**Fig. 5.** Survival difference according to status of the mitosis.

currence, one had high mitosis and small tumor size, one has low mitosis and large tumor size, and the other one had both high mitosis and large tumor size. Six patients had distant metastasis, all of them had high mitosis and four of them had large tumor size.

Imatinib was used in 9 patients with high risk and recurrent disease. Six (66.7%) of them had distant metastasis. Four (44.4%) patients had tumor regression after imatinib treatment. There were no patient in our series received sunitinib.

### Discussion

GIST may arise anywhere in GI tract. The most common site was stomach (60-70%), whereas colorectal GIST was rare (5%).<sup>1</sup> In the our series, 0.44% of all colorectal tumors were diagnosed to have GIST. The most common symptoms were bowel habit change (n = 10, 52.6%). Besides, rectal bleeding and abdominal pain were also found. The mean age of GIST patients was 61 ± 16.2 year-old which was similar to the previous result. According to the Fletcher’s criteria, tumors with low mitotic rate ( $\leq 5$  mitoses per HPF) or smaller size ( $< 2$  cm) had a low risk of metastasis.<sup>1</sup> In a study of 20 colonic stromal tumors, an infiltrative growth pattern in the muscularis propria, invasion of the mucosa, and high mitotic counts correlated significantly both with metastases and with death from tumor.<sup>10</sup> Our results showed that patients without any risk have less advanced disease and recurrence. Large tumor size ( $> 5$  cm) has higher risk of recurrence (100%).



**Fig. 6.** Survival difference according to the risks.

**Table 2. Risk stratify by tumor size and mitosis**

	n	%	Recurrence %	p
Risks(%)				
Low risk	7	37	0	
High risk	12	63	8 (66.7%)	0.006

Surgery is the treatment of choice for GISTs. In our study, 15 patients received radical surgery and 13 patients had R0 resection. The median survival of radical surgery were 35 ± 24.6 months in R0 resection, 44 months in R1 resection, and 5 months in R2 resection. Four patients received local resection and all of them had R0 resection. The median survival of local resection was 63 ± 43.1 months. The survival rate was better in local excision group (Fig. 3). The reason might be people who received radical surgery have larger tumor size ( $> 3$  cm in our series) and higher mitosis ( $\geq 5/50$  HPF).

Most of the patients in our series had spindle cell type in morphology (n = 16, 84.2%). The recurrent rate was 43.8% in spindle cell type. Only one patient with mixed cell type had local recurrence. The median survival of the patients with spindle cell type of the GIST was 40.5 ± 31.4 better than those with mixed cell type (19 ± 16 months). However, the case numbers were too small, and the comparison of the patients’ outcome associated with morphology was not reliable in our series.

GISTs rarely metastasize to lymph nodes, but often dissemination to the liver and peritoneum. Chemotherapy and radiotherapy are useless. Medical

treatment is based on non-selective tyrosine kinase inhibitors: imatinib and sunitinib.<sup>2</sup> Hassan I., et al. demonstrated that patients with high-risk colorectal GIST have higher risk of developing metastases and should be considered for adjuvant therapy with tyrosine kinase inhibitors.<sup>11</sup> Imatinib is indicated for the treatment of metastatic or unresectable GIST and as adjuvant therapy in patients with high-risk GIST.<sup>1,11</sup> It reliably achieves disease control in 70-85% of patients with advanced gastrointestinal stromal tumors.<sup>1</sup> In a double-blind, placebo-controlled trial, 8% patients in the imatinib group and 20% patients in the placebo group had tumor recurrence or had died after complete gross resection of primary GISTs at a median follow-up of 19.7 months. The author concluded that imatinib significantly improved recurrence-free survival compared with placebo (98% vs. 83% at 1 year,  $p < 0.0001$ ).<sup>12</sup> Sunitinib is second-line therapy, after imatinib failure.<sup>2</sup> In a double-blind, phase III trial, the median time to progression with sunitinib was 6.3 months versus 1.5 months with placebo.<sup>1</sup> In our study, nine (47%) of patients use imatinib due to metastasis or recurrence disease. All of them were high-risk patients and 44.4% of them had tumor regression after imatinib treatment. The response rate of imatinib in our series was lower than the other literature. The reasons might due to the case numbers were too small or most patients who received imatinib in our series had distant metastasis.

## Conclusion

Most colorectal GIST are located in the rectum. Patients with large tumor size (tumor size  $> 5$  cm, recurrent rate 100%) or high mitosis (mitosis  $\geq 5/50$  HPF, recurrent rate 63.5%) will have higher recurrent rate and mortality rate. Aggressive treatment or follow-up should be applied in high-risk patients.

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原 著

## 大腸直腸之胃腸道間質瘤之臨床病理表現及預後分析：單一醫療機構之分析

楊雪儷 張世慶 藍苑慈 王煥昇 楊純豪 姜正愷 陳維熊 林資琛 林楨國

台北榮民總醫院 外科部 大腸直腸外科

**目的** 大腸直腸之胃腸道間質瘤是一種罕見的大腸直腸腫瘤。它的發生主要是因為 c-kit 突變所造成的。這篇文章主要是要探討大腸直腸之胃腸道間質瘤，其臨床病理表現及預後。

**方法** 這是一個單一醫學中心，由單一外科團隊執行的研究。從 1997 年開始所有住院接受大腸腫瘤根除性切除手術的病人皆會接受評估是否符合於此一研究。診斷符合胃腸道間質瘤，也就是病理免疫染色 CD 117 呈陽性的病人，予以收錄至此一研究，並探討其臨床病理表現及預後。

**結果** 從 1997 年到 2008 年間，一共有 4205 位病患接受大腸腫瘤根除性切除手術。其中有 19 位 (0.44%) 診斷有胃腸道間質瘤。這 19 位病患平均年齡是  $61.3 \pm 16.2$  歲 (範圍：23-81 歲)。其中十四位 (74%) 是男性。有十四位病患 (74%) 腫瘤位於直腸。腫瘤平均直徑是  $4.0 \pm 3.3$  公分。最大的腫瘤有  $13 \times 7 \times 6$  公分。有十一個腫瘤顯示了高度分裂。十五名患者接受了根除性切除手術。九名患者接受了 imatinib 治療，這些患者包括腫瘤細胞屬於高度分裂，或腫瘤大小大於 5 公分，或腹腔內有腫瘤散播。平均追蹤時間是  $40.2 \pm 29.8$  個月 (範圍：3-111 個月)。在十一名腫瘤屬於高度分裂 ( $\geq 5/50$  HPF) 的患者中，有七名患者在 56 個月內復發。對於腫瘤屬於低度分裂的患者，存活率高達 87.5%，比腫瘤屬於高度分裂的患者存活率高 (54.6%)。另外，腫瘤屬於高風險的患者有比較高的風險產生腫瘤復發 (66.7%)。

**結論** 大腸直腸之胃腸道間質瘤若腫瘤大於 5 公分 (復發率：100%) 或是腫瘤分裂數大於 5/50 HPF (復發率：63.5%)，即使接受根除性手術切除，仍然會有較高的腫瘤復發率。

**關鍵詞** 胃腸道間質瘤、大腸直腸癌。