Case Analysis

Oncological Results for the Surgical Treatment of Rectal Gastrointestinal Stromal Tumor

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Key Words
Gastrointestinal stromal tumor;
Clinicopathology;
Rectum

Purpose. Primary gastrointestinal stromal tumor (GIST) of the rectum is rare and its clinico-pathology is not well understood. This study investigated the clinical characteristic of rectal GIST treated in a single institute.
Methods. From January 1990 to December 2007, medical records in our institute were reviewed and patients who underwent surgery for rectal GIST were identified. Their demographic features, tumor size, tumor location, clinical symptoms, operation methods, adjuvant treatment, recurrence, and survival were investigated and analyzed.
Results. Of the ten rectal GIST cases identified, nine were males. The median age at the time of diagnosis was 57 years (range: 38-82) and the median survival time was 23 months (range from 4 to 107 months). The major symptoms as an initial presentation were tenesmus, lower GI bleeding and palpable abdominal mass. The mean size of tumor was 9.3 cm (range: 3.2 to 15 cm). The overall 5-year survival rate was 38.1% and 5-year disease free survival rate in patients of complete resection was 21.4%. The five-year survival rate is 0% in non-curative resection patients and 42.9% in curative resection patient ($p = 0.24$). The five years survival rate is 0% in patients with tumor ≥ 10 cm and 60% in patients with tumor < 10 cm. ($p = 0.006$)
Conclusion. The most common symptoms of rectal GIST are tenesmus and lower GI bleeding, which are *similar* to those of other kinds of rectal tumors. The tumor size ≥ 10 cm is a risk factor of prognosis in rectal GIST. The appropriate treatment for rectal GIST is complete resection without residual tumors, with complete removal of metastases even in patients with recurrence. Future studies should focus on neo-adjuvant treatment strategies.
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Gastrointestinal stromal tumor (GIST) is a kind of stromal tumor that develops from gastro-intestinal (GI) mesenchymal cells from the esophagus to the rectum. Before 1990, most investigators thought these mesencgymal cell tumor to be the neoplasm from smooth muscle of gastrointestinal tract, and considered that these tumors were one kind of leiomyoma, leomyosarcoma or leiomyoblastoma.[1] With the advent of immuno-chemical staining and ultra-structural tissue examination, many physicians thought these tumors were another group of gastrointestinal mesenchymal tumors and it is different from the tumor from

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smooth muscle cell.[2] In 1998, Hirota and his colleagues found that these mesenchymal tumors express mutated gene of tyrosine kinase receptor and CD34 (The hematopoietic progenitor cell antigen) from interstitial cell of Cajal in GI tract and defined GIST as one kind of GI mesenchymal tumor.[3] Recently, many investigator found a few number of GIST without KIT mutations had gain-of-function mutations of PDGFRA (platelet-derived growth factor receptor alpha) which can bind to kit protein and lead to cellular proliferation and differentiation.[4] Currently, GIST is a specific group of mesenchymal tumors from the GI tract that express CD117 (C-kit proto-oncogene) and CD34.[5]

The most common site of GIST is the stomch, accounting for about 65% of GIST. The second most common site is the intestine (30-35%) while GIST from the esophagus, colon or rectum account for less than 5%.[6] Rectal GIST accounts for 0.1% of all tumors that originate from the rectum, with a reported incidence of 0.45 persons per 1,000,000 persons annually.[7] Due to its rarity, the clinico-pathology of rectal GIST is more obscure than those of gastric and intestinal GIST.

This study identified rectal GIST patients treated in a single institute from 1990-2007 and determined their clinico-pathologic characteristic, evaluated their treatments and analyzed their clinical outcomes.

Materials and Methods

We reviewed the pathology of leiomyoma and leomyosarcoma leiomyoblastoma and GI tract autonomic nerve tumor of rectum from January 1990 to December 2007 at National Taiwan University Hospital. We have routinely identified CD117 and CD34 antigen in GI tract mesenchymal tumor after 2000. We rechecked CD117 and CD34 in all specimen of mesenchymal tumor from rectal before 2000. The specimen that expressed CD117 and CD34 antigen was included. There were 356 patients with GI tract mesenchymal tumor from 1990 to 2007. Of them, 212 were in stomach, 129 were in small intestine and 4 were in colon and the other 11 were in rectum. One patient with rectal mesenchymal tumor had a diagnosis of leiomyoma without CD117 and CD34 expression. Finally, there were ten patients who diagnosed as rectal GIST from January 1990 to December 2007. Their demographic feartures, tumor size, tumor location, clinical symptoms, operation methods, adjuvant treatment, recurrence and survival were investigated and analyzed.

Surgical treatment was classified into curative and non-curative resection. Curative resection was defined as the complete tumor resection without residual tumor. Noncurative resection was defined as tumor not completely resected because of infiltration into major organs or vessels, or the presence of multiple metastases. Survival time was calculated from the operation date to the last day of follow-up or death. Local recurrence was defined as the reappearance of a tumor at the initial site of the primary tumor.

The disease-free survival rate and survival rate was estimated by Kaplan-Meier method.[8] The relationship of tumor size and treatment characteristics to outcomes was tested by univariate analysis using the log-rank test. A p value < 0.05 was considered statistically significant.

Results

Patient and tumor characteristics

The ten patients who diagnosed as rectal GIST from January 1990 to December 2007 was nine males and a female. The median age at presentation was 57 years (range: 38-82). The median follow up period was 23 months (range: 4-107 months).

The most common symptom reported at the time of primary presentation were tenesmus in seven patients, bloody stool in two and palpable mass in one. Preoperative biopsy was performed in six patients and only two patients had preoperative diagnosis of GIST. The distance from the anal verge to the location of the tumor was 5 cm in four patients, 6 cm in three patients, and 4 cm, 10 cm, and 12 cm in one patient (Table 1).

Treatment and pathological findings

Eight of ten patients underwent curative resection

Table 1. Clinical Characteristics

Case	Age/Sex	Primary symptoms	Curative resection	Operation method	Distance from anal verge	Tumor size (cm)	Cell type	Mitotic count (/50HPF)
1	60/M	Palpable abdominal mass	-	Tumor excision	10	15	Spindle	10
2	82/M	Tenesmus	+	APR	4	12	Spindle	7
3	74/M	Tenesmus	+	APR	5	9.5	Spindle	1.5
4	54/M	Tenesmus	+	LAR	5	8.5	Spindle	5
5	67/M	Bloody stool	-	Tumor excision	6	6.7	Spindle	2.5
6	76/F	Bloody stool	+	LAR	12	3.2	Spindle	6
7	48/M	Tenesmus	+	APR	5	15	Spindle	3
8	53/M	Tenesmus	+	APR	6	10	Spindle	4
9	49/M	Tenesmus	+	APR	5	4	Spindle	0.5
10	38/M	Tenesmus	+	APR	6	9	Spindle	1

(+): Positive, (-): Negative

and other two underwent non-curative resection. Six of the 8 patients with curative resection underwent abdominoperineal resection, while the other two patients underwent low anterior resection. Both patients with non-curative resection had tumor excision without free margins in specimen. The mean tumor size was 9.3 cm (range: 3.2 to 15 cm); and 4 patients had tumor size ≥ 10 cm and other 6 patients < 10 cm. The cell type in all patients was all spindle cell. Three patients had mitotic count more than 5/50 in high power field (HPF), 7 patients had mitotic count ≤ 5/50 HPF (Table 1). The five years survival rates in patients with mitotic count more than 5/50 HPF was 0 and 40% in patients with mitotic count ≤ 5/50 HPF, and the *P* value was 0.42.

Recurrence and survival

Three patients had no recurrence until the most recent follow up, while 7 had recurrence. In patients with curative resection, 5 patients had recurrence in follow up. Three patients had liver metastasis and one patient had no treatment after diagnosis of liver metastasis (Case 2); the other two had liver resection after diagnosis of liver metastasis (Case 9, 10). Two patients had local recurrence, and one patient treated the recurrent tumor by radiotherapy; the other had no treatment. In patients without curative resection, one patient treated the residual tumor by radiotherapy and the other treated by tyrosine kinase inhibitor. The five years survival rate was 0% in patients with tumor ≥ 10 cm and 60% in patients with tumor < 10 cm (p = 0.006) (Fig. 1).

The mean disease free survival was 26 months (range 4-50 months) in patients who underwent complete resection (Table 2) and the 5 years disease free survival rate in these patients was 21.4%. Five patients were still alive during the last follow up, others were dead due to the disease progression. The median survival time was 23 months (4-107 months) as shown in Table 2. The overall 5 years survival was 38.1%. The five years survival was 0% and 42.9% in the non-curative and curative resection patients (p = 0.24) (Fig. 2).

Discussion

The symptoms and signs of GISTs are non-specific and depend on the location and size of tumors.[9]

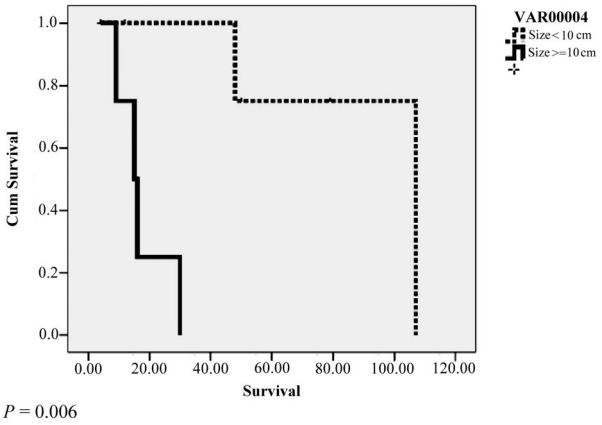

Fig. 1. Survival rate in tumor ≥ 10 cm and < 10 cm.

Table 2. Recurrence, survival and their management

Case	Recurrence	Recurrence site	Disease free (Months)	Management	Status	Survival (Months)
1		Noncurative resection		Radiotherapy	Dead	15
2	+	Liver	7	No treatment	Dead	9
3	-	-	48	-	Alive	48
4	-	-	4	-	Alive	4
5		Noncurative resection		Tyrosine kinase inhibitor	Alive	12
6	-	-	50	-	Alive	50
7	+	Local	11	Radiotherapy	Dead	30
8	+	Local	13	No treatment	Dead	16
9	+	Liver	49	Operation	Dead	107
10	+	Liver	31	Operation	Alive	79

(+): Positive, (-): Negative

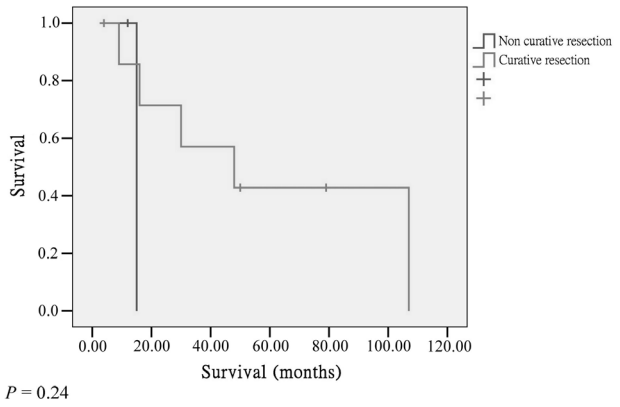

Fig. 2. Survival rate in curative resection and non-curative resection

In this and previous studies, the most common symptoms of rectal GIST are tenesmus, and lower GI bleeding.[10-12] The tumor can grow very large and occupy almost the entire pelvis, thereby causing tenesmus. Large tumors also usually undergo central necrosis, and resulting in tumor bleeding and lower GI bleeding. As such, their symptoms are no different from other rectal tumors.

Pre-operative histologic diagnosis is difficult in GIST patients. Since GIST is a kind of submucosal tumor, biopsy cannot easily be done via colonoscopy or proctoscopy. CT-guided biopsy is also not usually performed because of the risk of intra-abdominal seeding or tumor rupture. Histologic diagnosis is made only after surgical exploration and pathology examination. Colonoscopy or proctoscopy is used to differentiate these submucosal lesions from mucosal mass. Recently, endorectal ultrasound (EUS) has also been utilized in the pre-operative assessment of stromal rectal tumors, which provided more exact evaluation.[13]

The prognosis of GIST is mainly related to aggressive and complete surgical resection of the tumor. For this reason, en-bloc resection without tumor rupture is the treatment modality. The recurrence rate of rectal GIST is 68%-86% after local tumor excision, but is less than 20% with abdominoperineal resection.[9,14] If contiguous organ are involved, resection of the adjacent organ should also be performed if feasible.[15,16] Because there is no true capsule in the outer layer of GIST, tumor resection with a margin is necessary without en-nucleation.

In the studied patients, two patients without curative resection were not alive more than two years after operation, and their survival rate is less than patients who received curative resection. However, due to the small case number, the *p* value showed no significant difference. More large-scale studies are needed to achieve definitive conclusions.

Tumor size is another important factor in prognosis. According to several previous studies, patients with tumors larger than 5 cm in size had generally worse prognosis.[16-19] Large sized GISTs have greater propensity to invade to adjacent organs, which decreases the chances of performing radical resection, especially in the small pelvic space. In the two study patients with tumors ≥ 10 cm, local recurrence occurred shortly after surgery even though both underwent abdominoperineal resection (Case 7 and 8). The recurrence pattern in rectal GIST is much different from GIST in stomach and small intestine. The most recurrence site of gastric GIST or intestinal GIST is

liver then followed by peritoneum seeding.[20] Rectum is retroperitonium organ in pelvis with a small space. For this reason, there is no peritoneum seeding in our study but local recurrence occurred in these two patients (Case 7 and 8).

In contrast to colorectal adenocarcinoma, lymph node metastasis of GIST is very rare (< 10%), such that lymph node dissection is not necessary in rectal GIST surgery.[21]

Complete resection of isolated liver metastases plays an important role in prognosis. According to Chen et al, patients who underwent complete resection of liver metastases had a significantly longer survival than those who had incomplete resection.[22,23] Aggressive resection of metastatic tumor is considered a factor in patients with low-grade tumor initially but had longer disease-free interval. Two patients with liver metastases in this study had favorable prognosis after complete removal of the metastases. One survived for more than 100 months while the other was still alive by the end of study (Case 9 and 10).

The role of chemotherapy and radiotherapy for GIST is poor and controversial, and radiotherapy in this study showed the same result (Case 1 and 7).[24] However imatinib, a kit tyrosine kinase inhibitor used to treat patients with chronic myelocytic leukemia, has an effect on GISTs. In unresectbale or metastatic GISTs, more than 50% of patients have experienced different grades of tumor shrinkage after using imatinib.[25] Imatinib is now used for patients with incomplete tumor resection, tumor spillage, recurrence or metastasis, or in patients with other high risk factors.[25] In terms of neo-adjuvant therapy, only few reports have described using imatinib as an agent in the preoperative treatment of GIST.[26] Ebihara and colleagues reported a case with low rectal GIST that preserved anal function by preoperative imatinib therapy.[27] Neo-adjuvant therapy may play an important role in treating large rectal GIST, although more large-scale serial studies are still warranted to confirm the effects of imatinib as neo-adjuvant therapy.

Generally speaking, the 5-year overall survival of GIST is 41%-54%, but rectal GIST had lower 5-year survival rate of 20-25%.[25,28] The overall 5-year survival rate in the study is 38.1%. There is no many data regarding curative resection of rectal GIST because of the small case number of this series. Yeh and colleagues reported a non-randomized study of 40 patients who underwent curative resection of primary rectal GISTs. The overall 1-year, 3 years, and 5-year survival rates were 97%, 90%, and 75% and the 1 year, 3 years, and 5-year disease free survival rates were 90%, 59%, and 46%.[29] The 5-year survival and disease free survival rates were 42.9% and 21.4%, respectively, in the study patients with curate resection.

In conclusion, the most common symptoms of rectal GIST are tenesmus and lower GI bleeding, which are similar to those of other kinds of rectal tumors. Patients with larger tumor size has poor prognosis in rectal GIST. Appropriate treatment is complete resection without residual tumors, and complete removal of metastses should be performed if possible. Tyrosine kinase inhibitor may be used in patients with incomplete resection and metastatic tumors but more large-scale studies are needed to clarify the use of imatinib as neo-adjuvant therapy.

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病例分析

直腸的胃腸間質腫瘤在腫瘤外科之治療成果

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目的　直腸的原發性胃腸間質腫瘤是很少見的，且對於其臨床病理的認知也並不多。本研究爲調查並分析其在單一醫學中心之治療的成果，及其臨床表徵和治療的預後。

方法　以回溯性之方法從 1990 年至 2007 年，將所有在本院有接受外科手術治療的原發性直腸胃腸間質腫瘤，調查並分析其病人之特性、腫瘤大小、腫瘤位置、臨床症狀、手術方法、術後治療及術後存活。

結果　總共有十個病人接受外科的治療，這裡面有九個爲男性。年齡之中位數爲 57 歲 (範圍：38-82 歲)，追蹤時間的中位數爲 23 個月 (範圍：4 至 107 月)。其最主要的臨床表徵爲裡急後重、下消化道出血及腹部可觸摸到腫瘤。腫瘤大小的平均爲 9.3 公分 (範圍：3.2 至 15 cm)。所有的病人其五年存活率爲 38.1%，而接受腫瘤完全切除的病人其五年腫瘤非復發之存活爲 21.4% (p = 0.24)。接受腫瘤完全切除的病人其五年存活率爲 42.9%，而未完全切除的病人爲零。腫瘤大於等於 10 公分的病人其五年存活爲零而小於 10 公分的病人爲 60% (p = 0.006)。

結論　直腸胃腸間質腫瘤其主要症狀和一般的直腸腫瘤相似，是以裡急後重和下消化道出血來表現。腫瘤是否大於 10 公分對於預後是一個很重要的因子。直腸胃腸間質腫瘤的治療是以腫瘤完全切除爲主，如果有轉移其治療原則也盡可能將轉移切除，未來期待在術前化療能對其整體治療有所幫助。

關鍵詞　胃腸間質腫瘤、臨床病理、直腸。