Gastrointestinal Stromal Tumor of the Rectum: Report of Three Cases

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Gastrointestinal stromal tumors (GISTs) account for about 0.2% of all malignancy of gastrointestinal tumors and rarely arise in the rectum. We experienced three patients with large GISTs in the rectum. Case 1 (66-year-old man) underwent abdominoperineal resection (APR) for intrapelvic mass. The tumor was 90mm and diagnosed to be a Kit-positive GIST. Case 2 (81-year-old woman) underwent right hemicolectomy for concurrent ascending colon cancer by a local physician. In our Hospital, APR was performed for intrapelvic mass. The tumor was 90mm and diagnosed to be a Kit-positive GIST. Ten months after surgery, multiple liver tumors developed. She received oral imatinib for metastases. Case 3 (83-year-old woman) was yielded a diagnosis of Kit-positive GIST by a percutaneous biopsy. Imatinib was given preoperatively. However, adverse reactions occurred and the drug was withdrawn. APR was performed. The tumor was 70mm. At present, Case 1 and 3 patients are alive without recurrence.

Key words: gastrtointestinal stromal tumor, Rectum, Imatinib, Neoadjuvant therapy

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors derived from interstitial cells of Cajal, which reside in the muscularis of the gastrointestinal wall. GISTs account for about 0.2% of all malignancy of gastrointestinal tumors [1]. GISTs arise in the stomach in 60% to 70% of patients, the small intestine in 20% to 25%, the colon or rectum in 5%, and the esophagus in less than 5% [2]. These tumors often have metastasis or with recurrence after resection [3-6]. Tumor diameter and the number of mitotic figures have been proposed as predictors of biologic malignancy, but this remains to be established [7, 8]. Kit-positive GISTs have been reported to respond well to imatinib and sunitinib [9-13], and these drugs are now used to treat metastatic and recurrent GISTs and to prevent postoperative recurrence. Whether neoadjuvant chemotherapy is indicated for the treatment of large GISTs remains controversial. We describe our experience with 3 patients who underwent surgery for large GISTs of the rectum. One patient underwent surgery after neoadjuvant chemotherapy.
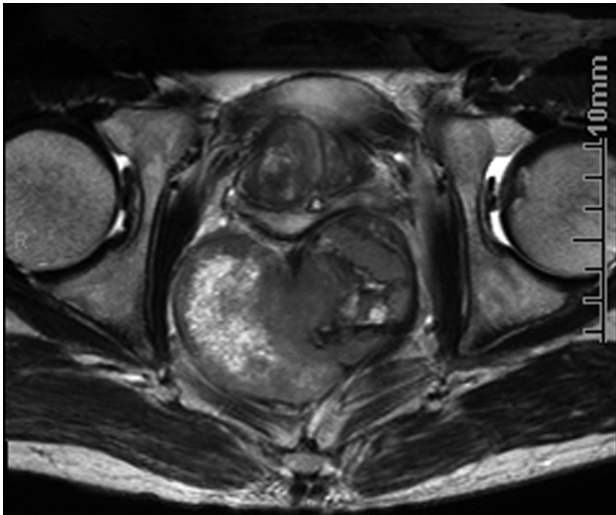
CASE 1

The patient was a 66-year-old man whose main symptom was anal pain. Right inguinal hernia repair was performed at the age of 63 years. The family history was irrelevant to the current disorder. The patient consulted a local physician because of anal pain in the beginning of August 2007. Colonoscopy revealed a submucosal-like mass in the rectum. Abdominal computed tomography (CT) showed an intrapelvic mass. In October, the patient was referred to our department for further evaluation and treatment.

On admission, the height was 168 cm, and the body weight was 58 kg. The palpebral conjunctiva was not anemic. The bulbar conjunctiva was not jaundiced. The abdomen was flat and soft. No mass was palpable. Rectal examination revealed an elastic hard, elevated mass with a smooth surface, about 8 cm in diameter, on the right side of the rectal wall 1 cm from the anal verge. Routine blood tests, serum chemical analysis, and urinalysis showed no abnormalities. As for tumor markers, the carcinoembryonic antigen level was slightly elevated (5.1 ng/mL). Colonoscopic biopsy failed to yield a definite diagnosis. CT and magnetic resonance imaging (MRI) revealed a relatively well-demarcated, submucosal mass, about 8 cm in diameter, in the posterior wall of the rectum. The tumor appeared to be heterogeneous, with no evidence of liver or lung metastasis (Fig. 1).

In November 2007, abdominoperineal resection was performed because the border between the tumor and the levator ani muscle was not clearly demarcated. The left colic artery was preserved. Lateral lymph-node dissection was not performed. Macroscopic examination of the resected specimen showed a submucosal-like tumor. The surface of the rectal mucosa was normal. The tumor, 90 x 80 x 55 mm, was elastic soft, with a thin capsule and a white cut surface. Histopathological examination showed that the tumor was located in the muscularis of the rectum and consisted of bundle-like proliferations of spindle-shaped cells (Fig. 2a). On immunohistochemical staining, the tumor was diagnosed to be a Kit-positive GIST (Fig. 2b). There were 12 mitotic figures per 50 high-power fields. A high-risk GIST was thus diagnosed . There was no evidence of

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Fig. 1 Magnetic resonance image (T2-weighted image) revealed about 8 cm mass in the posterior wall of the rectum. The tumor appeared to be heterogeneous. (Case 1)
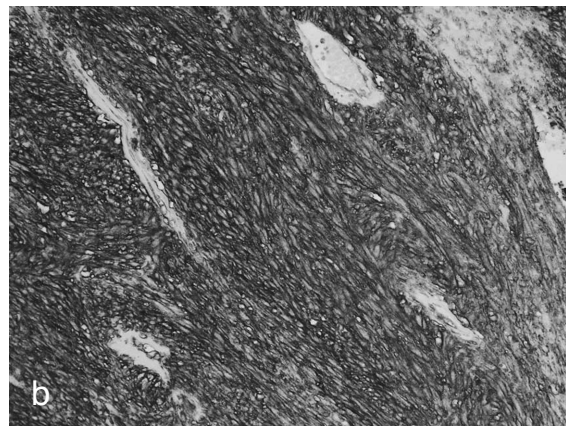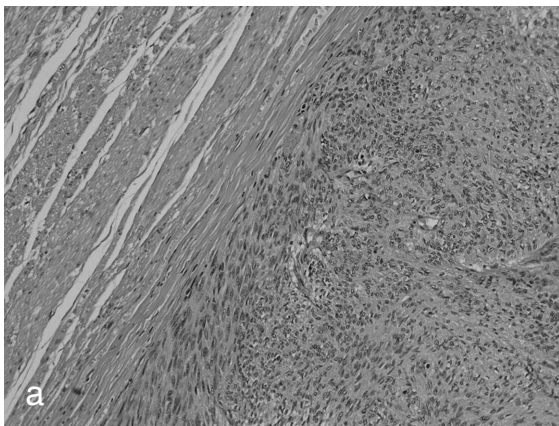
Fig. 2 （a）Histopathological examination showed that the tumor was located in the muscularis of the rectum and consisted of bundle-like proliferations of spindle-shaped cells. (Case 1)
（b）Immunohistochemical staining showed that the tumor from case 1 was positive for c-kit.

lymph-node metastasis.

CASE 2

The patient was an 81-year-old woman who presented with melena. She had a history of cerebral infarction in her 50's. The family history was irrelevant to the current disorder. In January 2009, the patient consulted a local physician because of melena. A tumor was found in the left side of the rectum. Colonoscopy showed an extramural mass in the rectum and type 2 colon cancer, 2.5 cm in diameter, in the ascending colon. Laparoscopic-assisted right hemicolectomy was performed to treat the cancer in the ascending colon. Histopathological examination revealed a stage IIIa moderately differentiated adenocarcinoma invading the muscularis propria (T2), with a single paracolic lymph-node metastasis. The patient was introduced to our hospital for further evaluation and treatment of the rectal tumor.

On admission, the height was 144 cm, and the body weight was 43 kg. The palpebral conjunctiva was not anemic. The bulbar conjunctiva was not jaundiced. The abdomen was flat and soft. No mass was palpable. Digital rectal examination revealed an elastic hard, smooth, elevated mass, about 10 cm in diameter, arising in the left side of the rectum 2.0 cm from the anal verge. On routine blood tests, the hemoglobin concentration was 10.9 g/dL. Serum chemical analysis and urinalysis showed no abnormalities. As for tumor markers, the carcinoembryonic antigen level was within the normal range. CT and MRI revealed no evidence of liver or lung metastasis. A relatively well-demarcated lobular mass, about 9 cm in diameter, was seen in the left wall of the rectum. The tumor consisted of a mixture of parenchymal and cystic elements (Fig. 3).

In March 2009, abdominoperineal resection was performed because the border between the tumor and the levator ani muscle was poorly demarcated. The left colic artery was preserved. Lateral lymph-node dissection was not performed. Macroscopic examination of resected specimens showed an extramural tumor. The surface of the rectal mucosa was normal. The tumor, 90 x 80 x 70 mm, had a thin capsule and was multinodular, with necrosis and bleeding at its center. The parenchymal portion of the tumor was elastic soft, with a white cut surface. Histopathological examination showed that the tumor was situated beneath the muscularis of the rectum. The lesion consisted of bundle-like proliferations of spindle-shaped cells. Immunohistochemical staining revealed a Kit-positive GIST. Five or less mitotic figures were present per 50 high-power fields. A moderate-risk GIST was thus diagnosed. There was no evidence of lymph-node me-
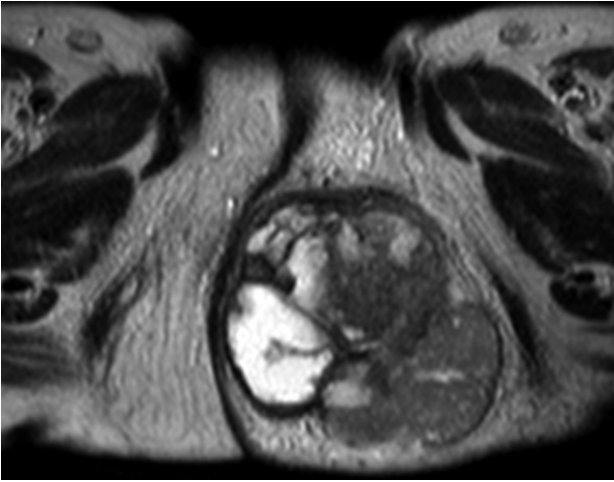
Fig. 3 Magnetic resonance image (T2-weighted image) revealed about 9 cm lobular mass in the left wall of the rectum. The tumor consisted of a mixture of parenchymal and cystic elements. (Case 2)
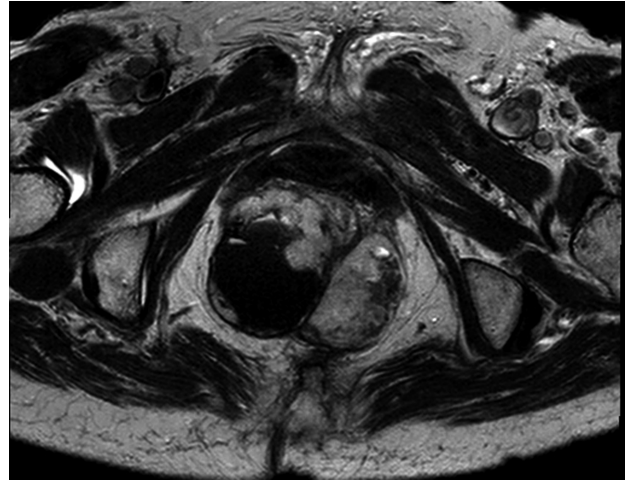
Fig. 4 Magnetic resonance image (T2-weighted image) revealed about 7 cm lobular mass, extending from the right wall to the dorsal side of the rectum. The tumor consisted of intermingled parenchymal and cystic elements. (Case 3)

tastasis.

After surgery, the patient was discharged from the hospital in good condition. Ten months after surgery, multiple liver tumors (9 mm in the dorsolateral segment of the left hepatic lobe [S3], 9 mm in the posteroinferior segment of the right hepatic lobe [S6], 8 mm in the posterosuperior segment of the right hepatic lobe [S7], 8 mm in the anterosuperior segment of the right [S8]) developed. Because the carcinoembryonic antigen level was not elevated. Liver tumors ware judged to be metastasis from GIST. We started chemotherapy with Imatinib and continued for 12 months up to now. The patient has stable disease.

CASE 3

The patient was an 83-year-old woman whose main symptom was anal pain. The past history and family history were not relevant to the current disorder. Early in January 2010, the patient consulted a local physician because of anal pain. Abdominal CT revealed a mass in the right side of the rectum, and the patient was referred to our hospital for further evaluation and treatment. A percutaneous biopsy yielded a diagnosis of Kit-positive GIST. Imatinib was given preoperatively to promote tumor shrinkage, increase the probability of curative resection, and preserve anal function. However, lower extremity edema and other adverse reactions occurred, and the drug was withdrawn. The patient was then admitted to the hospital to undergo surgery.

On admission, the height was 151 cm, and the body weight was 52 kg. The palpebral conjunctiva was not anemic, and the bulbar conjunctiva was not jaundiced. The abdomen was flat and soft. No mass was palpable. Digital rectal examination revealed an elastic hard, elevated mass with a smooth surface, about 7 cm in diameter in the right side of the rectum 2 cm from the anal verge. Routine blood tests, serum chemical analysis, and urinalysis showed no abnormalities. As for tumor markers, the carcinoembryonic antigen level was mildly elevated (7.7 ng/mL). Colonoscopy showed a submucosal-like mass in the lower rectum. A CT scan and MRI showed no evidence of liver or lung metastasis. There was a relatively well-demarcated, submucosal-like, lobular mass, about 7 cm in diameter, extending from the right wall to the dorsal side of the rectum. The tumor consisted of intermingled parenchymal and cystic elements (Fig. 4).

In May 2010, abdominoperineal resection was performed because of an unclear border between the tumor and the levator ani muscle. The left colic artery was preserved. Lateral lymph-node dissection was not performed. Macroscopic examination of the resected specimen showed a submucosal-like tumor. The surface of the rectal mucosa was normal. The tumor, 70 x 55 x 45 mm, was multinodular and had a thin capsule. Necrosis and bleeding were present at its center. The parenchymal portion of the tumor was elastic soft, and the cut surface was white. Histopathological examination showed that the tumor was located in the muscularis of the rectum and consisted of bundle-like proliferations of spindle-shaped cells. There were 18 mitotic figures per 50 high-power fields, indicating a high-risk GIST. There was no evidence of lymph-node metastasis. After surgery, the patient was discharged from the hospital in good condition. At present, the patient is alive without recurrence.

DISCUSSION

Rosai *et al.* [14] defined GISTs in the broad sense as epithelial tumors consisting of spindle-shaped cells or epitheloid cells that arise in the gastrointestinal tract and classified GISTs into 4 categories: 1) tumors with smooth-muscle differentiation (smooth muscle type), 2) tumors with neural differentiation (neural type), 3) tumors with smooth-muscle and neural differentiation (combined smooth muscle-neural type), and 4) tumors with no differentiation (uncommitted type). Rosai *et al.* defined uncommitted-type tumors as GISTs in the narrow sense. GISTs arise in the gastrointestinal wall and are positive for Kit receptors, a c-kit gene product that is expressed by interstitial cells of Cajal, which acts

Table 1   Patients characteristics

Case	Age(years)	sex	Location	Tumor size(mm)	Mitotic rate(/50HPF)	Risk classification Fletcer*	Risk classification Miettinen†
1	66	M	Rectum	90 x 80 x 55	12	high	high
2	81	F	Rectum	90 x 80 x 70	< 5	moderate	high
3	83	F	Rectum	70 x 55 x 45	18	high	high

* Fletcher's classicification [7]
† Miettinen's classicification [8]

as a pacemaker of neurotransmission between muscle fibers and nerve fibers in the gastrointestinal tract. GISTs are also positive for CD34, a marker of blood stem cells. GISTs are therefore thought to arise from interstitial cells of Cajal [4].

GISTs can be benign or malignant. Risk classifications have been proposed on the basis of criteria related to the risk of recurrence, rather than diagnosing a GIST with metastasis as malignant or a GIST without metastasis or recurrence as benign. Risk classification is based on a combination of factors such as tumor diameter and proliferative activity. In Fletcher's classification [7], the number of mitotic figures is used as an index of tumor-cell proliferative activity. Miettinen's classification [8] includes tumor location along with tumor diameter and the number of mitotic figures because outcomes are known to differ according to tumor location. Table 1 shows the risk classification in our patients. In Case 2, risk was classified as moderate according to Fletcher's classification because the number of mitotic figures was low. However, liver metastasis was diagnosed 6 months after surgery. The location of GISTs was thus suggested to be an important risk factor for recurrence that should be included in systems for risk classification proposed by Miettinen et al.

The treatment of choice for GISTs is complete resection [5, 6], particularly when complete resection can be achieved with a negative resection margin on macroscopic inspection [4]. The main routes of metastases from GISTs are hematogenous (liver metastasis) or peritoneal dissemination. Lymph-node metastasis is rare. Lymph-node dissection is thus not recommended, except when lymph-node metastasis is suspected [15].

Imatinib, an inhibitor of tyrosine kinases associated with the c-kit gene, is indicated for the treatment of unresectable, metastatic, and recurrent GISTs. In one series of patients with GISTs who received imatinib, Demetri et al. [9] obtained a disease control rate of higher than 80%. Although no patient had a complete response, 53.7% had a partial response, and 27.9% had stable disease. The response to imatinib has been reported to depend on the sites of mutations in the c-kit gene and platelet-derived growth factor receptor (PDGFRA) gene. In the B222 study (a phase II study of imatinib), c-kit gene mutational analysis was performed in 127 patients. The response rate was 83.5% in patients with mutations in exon 11 and 47.8% in those with mutations in exon 9, as compared with 0% in patients with no mutations in either the c-kit or PDGFRA genes [16].

At present, clinical studies of preoperative adjuvant chemotherapy with imatinib are ongoing. Consensus

has been reached that imatinib is indicated for the treatment of patients whose tumors are considered unresectable on preoperative evaluation and those in whom major surgery associated with functional disability must be avoided [5, 6]. Scaife et al. [17] obtained a response rate of 38% among 126 patients with unresectable GISTs who received imatinib. After treatment 17 patients could undergo surgery. Another study reported that preoperative treatment with imatinib to promote tumor shrinkage allowed anal function to be preserved in some patients with rectal GISTs [18]. Analysis of mutation sites in the c-kit or PDGFR genes on preoperative biopsy is expected to improve the ability to predict the therapeutic response to imatinib. However, because the rate of response to preoperative adjuvant chemotherapy with imatinib is about 40% [17], resection may not be feasible or noncurative resection may have to be performed in the majority of patients.

A phase II clinical trial (RTOG study s-0132) has assessed the therapeutic usefulness of preoperative adjuvant chemotherapy with imatinib in 30 patients with primary GISTs and 22 with recurrent GISTs [19]. In the study group as a whole, 5.8% of the patients had a partial response, and 87.0% had progressive disease. The resection margin was negative (R0) in 31 (69%) of the 45 patients who received surgery of the preoperative chemotherapy. Grade 3 or higher adverse events occurred in 35% patients. These results suggested that preoperative treatment with imatinib is feasible in patients with GISTs. However, the value of these initial findings is limited by the small numbers of patients studied and the use of postoperative adjuvant chemotherapy. Large clinical studies are needed to draw firm conclusions. All 3 of our patients had large tumors, reaching the anal verge. The preservation of anal function was therefore considered difficult, even after preoperative chemotherapy. Case 3 received imatinib preoperatively in the hope of promoting tumor shrinkage in the rectum, improving chances for cure, and preserving anal sphincter. However, treatment was discontinued because of adverse events.

The North American Intergroup phase III trial ACOSOG Z9001 [20] reported outcomes of postoperative adjuvant chemotherapy with imatinib. One-year postoperative adjuvant chemotherapy with imatinib (400 mg daily) was well tolerated and prolonged recurrence-free survival. The Scandinavian SSGXVIII study and the European Organization for Research and Treatment of Cancer (EORTC) 62024 study are now in progress to determine the optimal duration of treatment with imatinib. The results of these studies are awaited. We recommended Case 1 and 3 to receive

postoperative adjuvant chemotherapy with imatinib, but they refused treatment. Case 2 concurrently had stage IIIa colon cancer and liver metastasis appeared 10 months after surgery. Liver metastasis from GIST was diagnosed, with no elevation of tumor markers. The patient was given imatinib and currently has stable disease.

CONFLICT OF INTEREST STATEMENT

Toshiyuki Suzuki and other co-authors have no conflict of interest.

REFERENCES

1) Spivach A, Zanconati F, BonifaciocGori D, Pellegrino M, Sinconi A. Storomal tumors of small intestine (GIST). Prognostic difference based on clinical, morphological and immunophenotypic features. Minerva Chir. 1999; 54: 717‒24.

2) Miettinen M, Lasota J. Gastrointestinal stromal tumors definition, clinical, histological, immunohistchemical, and molecular genetic fetures and differential diagnosis. Virchows Arch. 2001; 438: 1‒12.

3) Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. Cancer. 1992; 69: 1334‒41.

4) Dematteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000; 231: 51‒8.

5) Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, *et al*. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw. 2010; 8 Suppl 2: S1‒41.

6) ESMO Guidelines Working Group, Blay JY, Le Cesne A. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2007; 18 Suppl 2: ii27‒9.

7) Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, *et al*. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002; 33: 459‒65.

8) Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23: 70‒83.

9) Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002; 347: 472‒80.

10) Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, *et al*. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004; 364: 1127‒34.

11) Zalcberg JR, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay JY, *et al*. EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group; Australasian Gastrointestinal Trials Group. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer. 2005; 41: 1751‒7.

12) Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, *et al*. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006; 368: 1329‒38.

13) Nishida T, Takahashi T, Miyazaki Y. Gastrointestinal stromal tumor: a bridge between bench and bedside. Gastric Cancer. 2009; 12: 175‒88.

14) Rosai J. Stromal tumors. In: Ackerman's Surgical Pathology. 8th ed, Mosby-Year Book, St Luis, Chicago, 1996: 645‒7, 6913.

15) Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg. 1993; 217: 72‒7.

16) Heinrich MC, Coress CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, *et al*. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003; 21: 4342‒9.

17) Scaife CL, Hunt KK, Patel SR, Benjamin RS, Burgess MA, Chen LL, *et al*. Is there a role for surgery in patients with "unresectable" c-KIT + gastrointestinal stromal tumors treated with imatinib mesylate ? Am J Surg. 2003; 186: 665‒9.

18) Lo SS, Papachristou GI, Finkelstein SD, Conroy WP, Schraut WH, Ramanathan RK. Neoadjuvant imatinibu in Gastointestinal stromal tumor of the rectum: report of a case. Dis Colon Rectum. 2005; 48: 1316‒9.

19) Eisenberg BL, Harris J, Blanke CD, Demetri GD, Heinrich MC, Watson JC, *et al*. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol. 2009; 99: 42‒7.

20) Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, *et al*. American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373: 1097‒104.