


CASE REPORT

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Liver metastases 2 years after resection of a very-low-risk duodenal gastrointestinal stromal tumor: a case report

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors, but are the most common mesenchymal tumors of the gastrointestinal tract. The risk classification of GISTs is based on the tumor size, mitotic index, tumor site, and presence of tumor rupture. Recurrence in the very-low-risk group is extremely rare. We herein report a case of liver metastases 2 years after resection of a very-low-risk duodenal GIST.

Case presentation: A 57-year-old woman presented to the hospital for evaluation of melena. Esophagogastroduodenoscopy showed bleeding from the exposed blood vessels at the top of a submucosal tumor approximately 20 mm in size located in the second (descending) part of the duodenum, and the bleeding was controlled with electrocoagulation. A GIST was suspected, and the patient underwent wedge resection of the duodenum. The resected specimen contained a 16- × 12-mm (< 20-mm) white submucosal tumor composed of spindle cells with a mitotic count of 4 per 50 high-power fields, and a histologically negative margin was achieved. Immunohistochemical analysis revealed positive tumor staining for c-kit protein and alpha-smooth muscle actin and negative staining for CD34, desmin, and S-100 protein. Therefore, the tumor was diagnosed as a very-low-risk duodenal GIST based on the Fletcher classification and modified Fletcher classification (Joensuu classification). The postoperative course was uneventful, and the patient was discharged on postoperative day 11. At the follow-up visit 2 years postoperatively, contrast-enhanced computed tomography revealed liver tumors in S8 and S6 measuring 26 × 24 and 10 × 10 mm, respectively. Both lesions showed peripheral dominant hyperenhancement with hypoenhancement inside, indicating tissue degeneration within the tumors. These imaging findings closely resembled those of the duodenal GIST. Hence, the patient was diagnosed with liver metastases of GIST 2 years postoperatively. She was subsequently started on treatment with 400 mg of imatinib. At the time of this writing (2 months after diagnosis), the patient was clinically well and asymptomatic and was continuing imatinib therapy.

Conclusions: Recurrence of very-low-risk GISTs is extremely rare. Even a small GIST with low mitotic activity can never be considered completely benign, and long-term follow-up is necessary.

Keywords: GIST, Imatinib, Mitotic rate

Background

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors, but they are the most common mesenchymal tumors of the gastrointestinal tract. The risk classification of GISTs is based on the tumor size, mitotic

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index, tumor site, and presence of tumor rupture. Recurrence of very-low-risk GISTs is quite rare. We herein present an extremely rare case of recurrence of a very-low-risk duodenal GIST.

Case presentation

A 57-year-old woman with type 2 diabetes mellitus presented to another hospital for evaluation of melena. Her clinical evaluation findings were unremarkable; however, laboratory examination demonstrated a low hemoglobin level of 9.9 g/dL. All other routine hematological and biochemical profiles were within the reference ranges. Contrast-enhanced computed tomography (CT) showed extravasation arising from a mass of high signal intensity in the second part of the duodenum (Fig. 1). Esophago-gastroduodenoscopy showed bleeding from the exposed blood vessels at the top of the submucosal tumor, which was approximately 20 mm in size and located in the second (descending) part of the duodenum; the bleeding was controlled with electrocoagulation (Fig. 2A–C). Endoscopic ultrasonography showed a 16.6-mm hypoechoic lesion arising from muscularis propria layer on the posterior wall of the descending duodenum (Fig. 2D). Fine needle aspiration biopsy was not performed because of the risk of rebleeding. A GIST was suspected, and the patient was referred to our hospital for surgical intervention. The tumor was detected on the posterior wall of the descending duodenum, protruding outside the serosal surface. After mobilization from the first to third portion of the duodenum using the Kocher maneuver, wedge resection was performed, and the duodenal wall was closed with sutures. The operation time was 110 min, and the blood loss volume was 50 mL. The resected specimen contained a 16- × 12-mm white submucosal tumor. Histopathological evaluation showed that the tumor was composed of spindle cells with a mitotic count of 4 per 50

high-power fields (HPFs) and that a histologically negative margin had been achieved. Hemorrhage and necrosis of the tumor were also observed. Immunohistochemical analysis revealed positive tumor staining for c-kit protein and alpha-smooth muscle actin and negative staining for CD34, desmin, and S-100 protein (Fig. 3). Therefore, the tumor was diagnosed as a very-low-risk duodenal GIST based on the Fletcher classification and the modified Fletcher classification (Joensuu classification). Furthermore, the tumor was classified as no-risk according to the Miettinen classification. The postoperative course was uneventful, and the patient was discharged on postoperative day 11.

Follow-up included physical examination every 3 months, and abdominal ultrasonography and CT scan every 6 months. At the follow-up visit 2 years postoperatively, abdominal ultrasound showed two heterogeneous hyperechoic lesions in the liver: a 25-mm mass in S8 and a 10-mm mass in S6. There was no increase in the tumor markers for hepatocellular carcinoma or gastrointestinal cancer. Contrast-enhanced CT revealed liver tumors in S8 and S6 measuring 26 × 24 mm and 10 × 10 mm, respectively (Fig. 4). Both lesions showed peripheral dominant hyperenhancement with hypoenhancement inside, indicating tissue degeneration within the tumors. There was no local recurrence in the duodenum after surgery. Magnetic resonance imaging showed hypervascular tumors with restricted diffusion and low apparent diffusion coefficients; they contained tissue degeneration within them, and they measured 25 × 21 mm and 10 × 8 mm in S8 and S6, respectively. The imaging findings of both tumors closely resembled those of the duodenal GIST. Hence, the patient was diagnosed with liver metastases of GIST 2 years postoperatively. She was subsequently started on treatment with 400 mg of imatinib. At the time of this writing (2 months

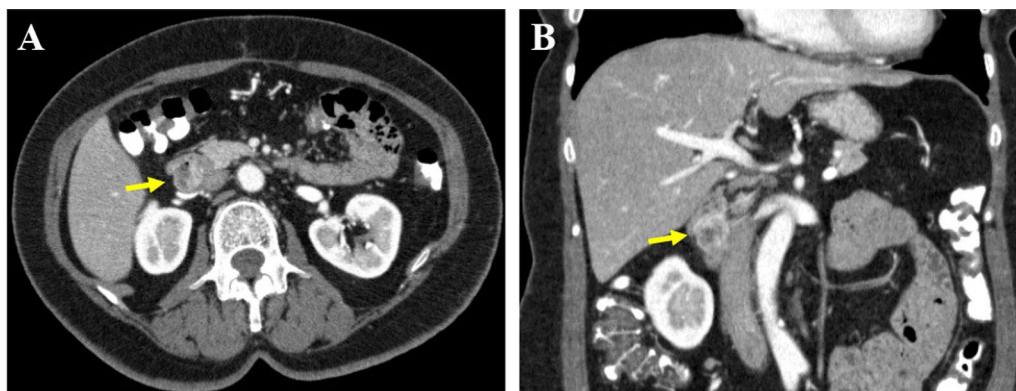


Fig. 1 A, B Contrast-enhanced computed tomography at the first visit. Extravasation was seen from a 20-mm mass in the second part of the duodenum (arrow)

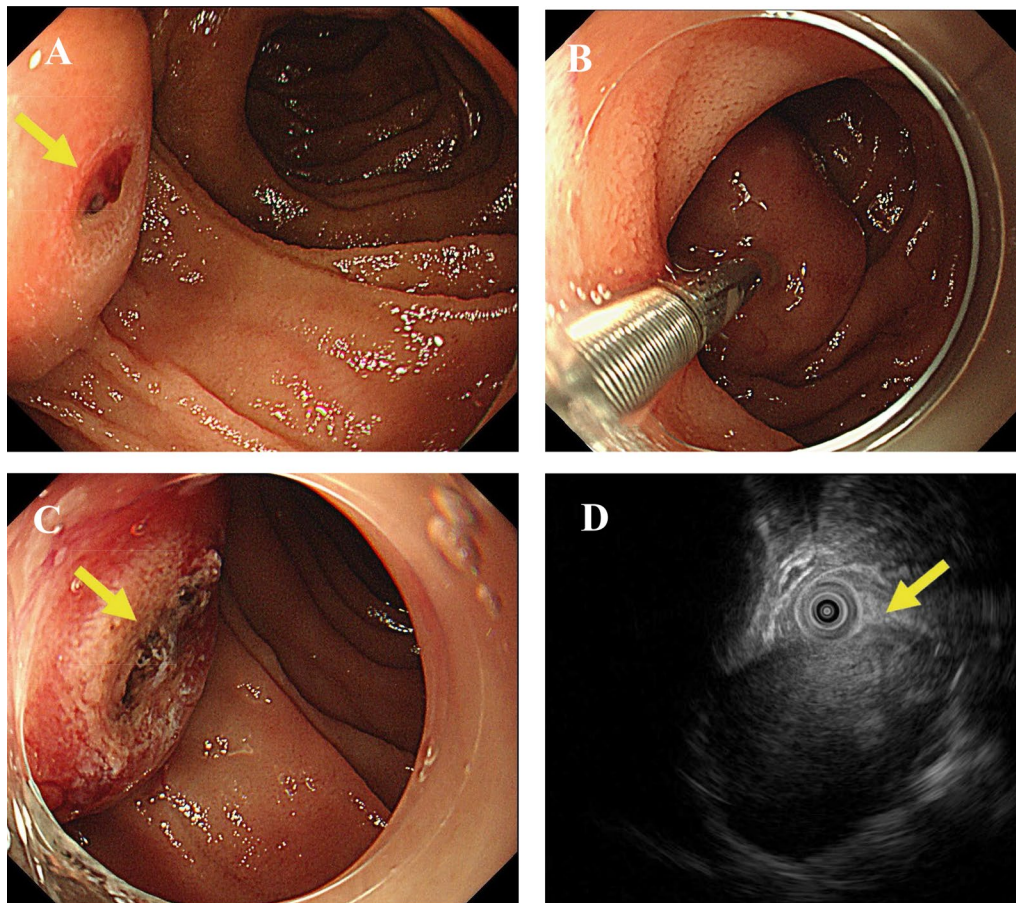


Fig. 2 **A** Esophagogastroduodenoscopy showed bleeding from the exposed blood vessels at the top of the 20-mm submucosal tumor in the second part of the duodenum (arrow). **B, C** The bleeding was successfully controlled with electrocoagulation (arrow). **D** Endoscopic ultrasonography showed a 16.6-mm hypoechoic lesion originating from the fourth layer of the duodenal wall (arrow)

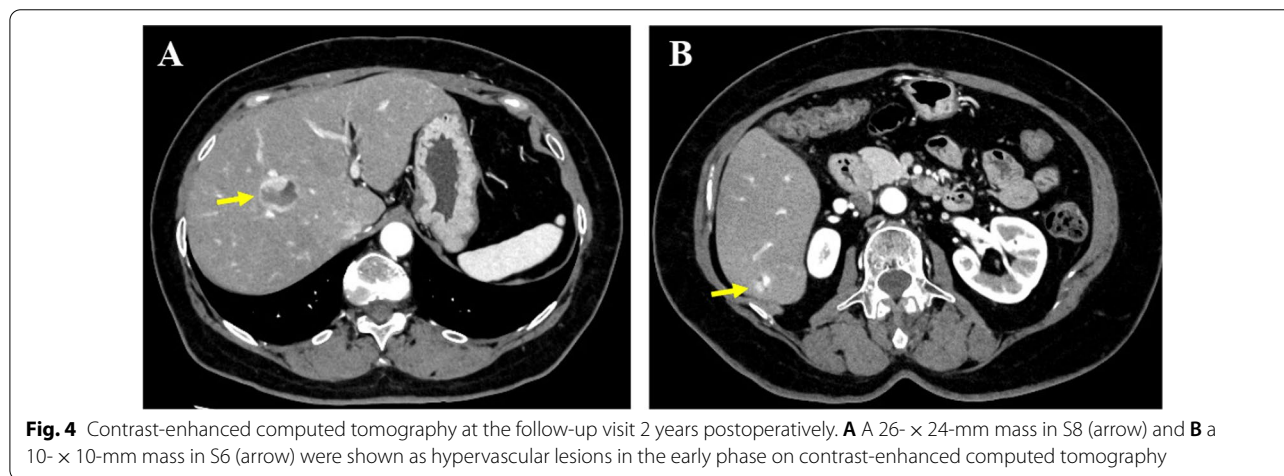
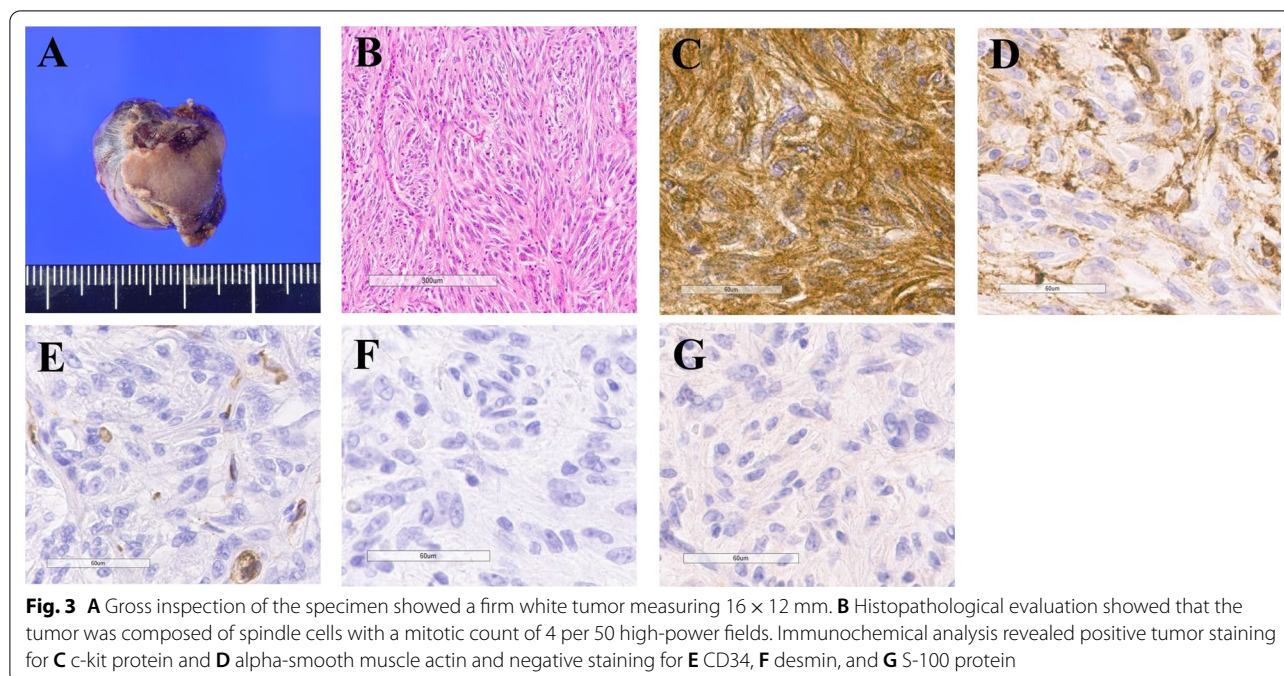
after diagnosis), the patient was clinically well and asymptomatic and was continuing the imatinib therapy.

Discussion

GISTs are rare mesenchymal tumors and can arise anywhere from the interstitial cells of Cajal at the submucosal and myenteric plexus of the gastrointestinal tract. They are the most common mesenchymal tumors of the gastrointestinal tract; approximately 60% of them originate in the stomach, followed by the small bowel (30%), rectum (5%), and duodenum (<5%) [1, 2]. The symptoms of GISTs are variable, and the clinical presentation includes diffuse abdominal pain, bleeding, fever, and obstruction. Histologically, GISTs are often divided into spindle cell types and epithelioid cell types. They have a characteristic immunohistochemical pattern in that CD117, which is part of the c-kit tyrosine kinase receptor, is positive in >95% of cases. Expression of CD34 occurs in >80% of GISTs, and alpha-smooth muscle actin is demonstrable

in about 25% [3, 4]. The standard treatment for GISTs is surgical resection with negative margins; however, the optimal margin width has not been defined. Local recurrence or metastasis occurs in approximately 40% of cases after curative resection, with liver metastasis being the main recurrence pattern of GISTs [5]. The kit inhibitor imatinib is the standard first-line therapy for recurrence following resection of primary GISTs.

Duodenal GISTs constitute <5% of GISTs and mostly occur in the second part of the duodenum, followed by the third, fourth, and first part [1]. The most common clinical presentation of duodenal GISTs is bleeding or abdominal pain [2]. Unlike other types of GISTs, the optimal surgical procedure for duodenal GISTs has not been definitively determined. In the stomach, the most common site of GISTs, limited resection is technically simple in most cases; in the duodenum, however, local resection can be more complicated. Pancreatoduodenectomy may even be performed when the tumor is located



in the descending part of the duodenum or involves the ampulla of Vater and pancreatic head. Nillson et al. [6] reported that low-risk gastric GISTs carry a 1.9% risk of recurrence, whereas low-risk duodenal GISTs have an 8.3% recurrence rate. Duodenal GISTs are often large at the time of diagnosis and tend to be located in the muscle layer and grow into the submucosa, resulting in both ulceration and hemorrhage. These factors are related to a higher malignant potential than that of gastric GISTs, though no specific gene products have been identified to account for the prognostic differences [7, 8].

According to the literature, several risk stratifications have been proposed: the Fletcher classification, the

modified Fletcher classification (Joensuu classification), and the Miettinen classification. The Fletcher classification is based on tumor size and mitotic index. It subdivides tumors into very low risk (tumor size of < 2 cm and mitotic count of < 5 per 50 HPFs), low risk (tumor size of 2–5 cm and mitotic count of < 5 per 50 HPFs), intermediate risk (tumor size of < 5 cm and mitotic count of 6–10 per 50 HPFs, or tumor size of 5–10 cm and mitotic count of < 5 per 50 HPFs), and high risk (tumor size of > 5 cm and mitotic count of > 5 per 50 HPFs, tumor size of > 10 cm and any mitotic index, or tumor of any size and mitotic count of > 10 per 50 HPFs) [9]. The modified Fletcher classification includes

the tumor site and presence of rupture as additional variables [10]. The Miettinen classification is based on tumor size, mitotic index, and location (Table 1) [11]. In the present case, the tumor in the duodenum was 16 mm in size and had a mitotic count of 4 per 50 HPFs; it was therefore classified as very low risk according to the Fletcher classification and the modified Fletcher classification and as no risk based on the Miettinen classification. In patients who have undergone complete resection of no-risk, very-low-risk, or low-risk GISTs, follow-up by abdominal CT is recommended every 6 months for 5 years after surgery [12]. Recurrence in the very-low-risk group is extremely rare, and even in the low-risk group, recurrence is quite rare (2.4%) after complete surgical removal [6]. To the best of our knowledge, only one other case report of postoperative recurrence of a very-low-risk GIST has been published to date [13]. In that case, suture-line recurrence at the gastrojejunal anastomosis appeared 8 years after resection; this might be considered local recurrence after surgery. In our case, the liver metastases appearing 2 years after surgery were classified as distant metastases, and this could be the first report of distant metastases of a very-low-risk GIST after radical resection. In addition to the prognostic factors used in the classifications, several other prognostic factors have been reported. From a clinical and histological viewpoint, tumor necrosis, hemorrhage, mucosal ulceration, and vascular invasion are associated with a poor outcome [14, 15]. The CT findings that suggest a malignant potential include a lesion larger than 11.1 cm, an irregular surface, an unclear boundary, the presence of invasion, heterogeneous enhancement, and wall invasion of other organs [16]. In our case, although categorized as very low risk, the GIST had several other malignant features such as heterogenous enhancement, hemorrhage, and tumor necrosis. The patient had not received adjuvant chemotherapy as there was no evidence of its

effect on very-low-risk GISTs [17]. The benefit of adjuvant chemotherapy for very-low-risk GISTs with those other malignant features remains unclear. Further data accumulation and its analysis could help to assess whether adjuvant chemotherapy should be given in such cases.

Besides the size, mitotic activity, and location of the tumor, several other factors are also related to the malignant potential of GISTs. Therefore, even a small duodenal GIST with low mitotic activity can never be considered as entirely benign, and long-term follow-up is still important.

Conclusions

We have herein reported an extremely rare case of recurrence of a very-low-risk GIST. Even subtle GISTs can never be considered as truly benign, and long-term follow-up is necessary.

Abbreviations

GIST: Gastrointestinal stromal tumors; EGD: Esophagogastroduodenoscopy; HPF: High-power fields; SMA: Smooth muscle actin; CE-CT: Contrast-enhanced computed tomography; Hb: Hemoglobin; MRI: Magnetic resonance imaging; HPFs: High-power fields.

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Author contributions

JM and KT reported the case and wrote the manuscript. KT, and KI were engaged in the patient's care including the surgery. SN, JT, KS, HM, TO, FY, KI, HT, and KK helped in drafting the manuscript. SH and KF participated in revising the manuscript critically. All authors have read and approved the final manuscript for publication.

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Availability of data and materials

The authors declare that all the data in this article are available within the article.

Table 1 Miettinen classification [11]

Mitotic counts/50 HPFs	Size (cm)	Stomach (predicted malignant potential)	Ileum (predicted malignant potential)	Duodenum (predicted malignant potential)	Colon (predicted malignant potential)
≤ 5	≤ 2.0	None	None	None	None
≤ 5	2.1–5.0	Very low	Low	Low	Low
≤ 5	5.1–10.0	Low	Moderate	Insufficient data	Insufficient data
≤ 5	> 10.0	Moderate	High	None	High
> 5	≤ 2.0	None	High	None	High
> 5	2.1–5.0	Moderate	High	High	High
> 5	5.1–10.0	High	High	Insufficient data	Insufficient data
> 5	> 10.0	High	High	High	High

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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References

- Beham A, Schaefer IM, Cameron S, von Hammerstein K, Füzesi L, Ramadori G, Ghadimi MB. Duodenal GIST: a single center experience. *Int J Colorectal Dis.* 2013;28:581–90.
- Miettinen M, Kopczynski J, Makhlof HR, Sarlomo-Rikala M, Gyorffy H, Burke A, Sobin LH, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. *Am J Surg Pathol.* 2003;27:625–41.
- Steigen SE, Eide TJ. Gastrointestinal stromal tumors (GISTs): a review. *APMIS.* 2009;117:73–86.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch.* 2001;438:1–12.
- 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.
- Nilsson B, Bümbling P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer.* 2005;103:821–9.
- Tornillo L. Gastrointestinal stromal tumor - an evolving concept. *Front Med (Lausanne).* 2014;1:43.
- Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2008;19(Suppl 2):iii35–38.
- Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002;33:459–65.
- Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol.* 2008;39:1411–9.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23:70–83.
- Blay JY, Bonvalot S, Casali P, Choi H, Debiec-Richter M, Dei Tos AP, Emile JF, et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO. *Ann Oncol.* 2005;16:566–78.
- Papalambros A, Petrou A, Brennan N, Bramis K, Felekouras E, Papalambros E. GIST suture-line recurrence at a gastrojejunal anastomosis 8 years after gastrectomy: can GIST ever be described as truly benign? A case report. *World J Surg Oncol.* 2010;8:90.
- Yi M, Xia L, Zhou Y, Wu X, Zhuang W, Chen Y, Zhao R, et al. Prognostic value of tumor necrosis in gastrointestinal stromal tumor: a meta-analysis. *Medicine (Baltimore).* 2019;98: e15338.
- Liu Q, Li Y, Dong M, Kong F, Dong Q. Gastrointestinal bleeding is an independent risk factor for poor prognosis in GIST patients. *Biomed Res Int.* 2017;2017:7152406.
- Tateishi U, Hasegawa T, Satake M, Moriyama N. Gastrointestinal stromal tumor: correlation of computed tomography findings with tumor grade and mortality. *J Comput Assist Tomogr.* 2003;27.
- The GIST Guideline Subcommittee of the Clinical Practice Guideline Committee for Cancer of JSCO, editors. Japanese clinical practice guidelines for GIST (4th edn). Kanehara, Tokyo; 2022.

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