

## Original Article

# Concurrent gastrointestinal stromal tumor and digestive tract carcinoma: a single institution experience in China

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**Abstract:** The aim of this study was to review the clinicopathological characteristics and survival outcomes of patients with concurrent gastrointestinal stromal tumor (GIST) and digestive tract carcinoma. Among 585 patients diagnosed with GIST from January 2005 to July 2014, 32 (5.5%) had synchronous digestive tract carcinoma, including 19 (59.4%) men and 13 (40.6%) women. The median age was 64 years (range, 43-84). GIST was located in the stomach (n=24), small intestine (n=6), duodenum (n=1) and retroperitoneum (n=1). GISTs were intra- or postoperatively discovered (n=28) or preoperatively identified (n=4). The tumor size was less than 10 mm (microGIST) in 23 (71.9%) GIST patients. The preoperatively identified GIST subgroup showed a significantly larger tumor size, more mitotic figures and a higher risk grade than the intra- or postoperatively identified GIST subgroup. Concurrent digestive tract carcinomas were most frequently located in the stomach (24 cases, 75%). The other involved sites were the esophagus (n=5), duodenum (n=2) and colon (n=1). With a median follow-up of 32 months (range, 9-80), 24 patients were alive without evidence of disease, 6 patients had died of carcinoma progression, 1 patient had died from an accident, and 1 patient experienced GIST metastasis to the liver. In summary, we discovered that 5.5% of GIST patients also developed a concurrent digestive tract carcinoma in a series of 585 GIST cases. The majority of GISTs are incidentally identified microGISTs. The concurrent carcinoma seems to have a greater unfavorable effect on prognosis than the GIST. However, for a GIST that is identified preoperatively with a high risk of progression, adjuvant therapy is warranted.

**Keywords:** Gastrointestinal stromal tumor, synchronous neoplasms, digestive tract malignancies, prognosis

## Introduction

Gastrointestinal stromal tumor (GIST) is rare, accounting for <1% of all gastrointestinal neoplasms, but it is the most common mesenchymal neoplasm of the gastrointestinal tract [1-3]. Once thought to be leiomyoma or leiomyosarcoma, GIST is now recognized as a distinct entity, due to its origin in Cajal cells and its characteristic activating mutation in c-KIT or, less frequently, in platelet-derived growth factor receptor  $\alpha$  [4-6]. In most cases, GIST develops in the stomach and small intestine, but it can occur in the rectum or mesentery. The median age at GIST diagnosis is approximately 60 years [6]. Abdominal pain and gastrointestinal bleeding are the most common clinical manifestations of GIST [7]. Currently, surgical resection is the standard curative treatment, and imatinib me-

sylate is the standard first-line treatment for unresectable or metastatic GIST [8].

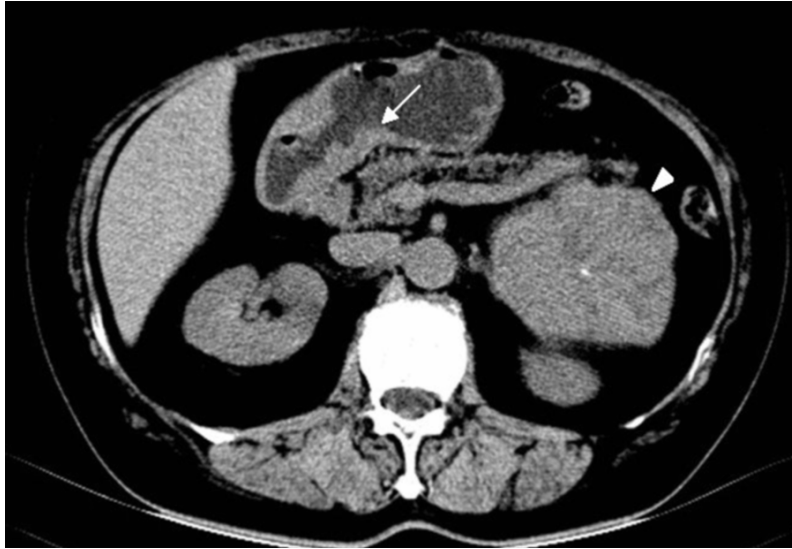
Since Maiorana [9] first reported coexistent epithelial and stromal tumors in the stomach in 2000, the coexistence of GIST with other malignancies, gastrointestinal or otherwise, has been reported with increasing frequency [10, 11]. Among the concurrent malignancies, those of gastrointestinal origin are the most common [6]. However, most of these publications are reports of single cases. Little is known about concurrent GIST and digestive tract carcinoma. Here, we present a series of 32 patients diagnosed with concurrent GIST and digestive tract carcinoma with the aim of investigating the clinicopathological characteristics and survival outcomes of patients with this rare disease at a single center in Wuhan, China.

## Concurrent GIST and digestive tract carcinoma

**Table 1.** Clinicopathological characteristics of 4 cases of preoperatively identified concurrent GIST and digestive tract carcinoma

No.	Sex/Age	Symptom	Clinical tests	GIST			Carcinoma			Surgery	Adjuvant imatinib	Follow up (months)	Outcome
				Location	Size (mm)	Mitosis (per 50 HPFs)	Location	Type	TNM/stage <sup>1</sup>				
1	F/64	Epigastric pain	CT: a giant retroperitoneal mass and gastric wall thickening; gastroscopy: antral ulcer	Retroperitoneum	120	4	Gastric antrum	Poorly differentiated adenocarcinoma	T3N1M0/II b	Distal gastrectomy and resection of the retroperitoneal tumor	1 year	12	Alive without disease
2	F/72	Melena	Colonoscopy: a mass in the right colon; EUS: gastric protrusion in the antrum	Gastric antrum	65	0	Right colon	Moderately differentiated adenocarcinoma	T1N0M0/I	Laparoscopic gastric wedge resection and right hemicolectomy	1 year	20	Alive without disease
3	F/66	Epigastric pain	Gastroscopy: a mass in the esophagus; CT: a protrusion in the gastric cardia	Gastric cardia	30	6	Esophagus	Moderately differentiated squamous cell carcinoma	T1N0M0/I	Esophagogastrectomy	No	17	Liver metastases 6 months after surgery
4	M/63	Abdominal discomfort	Gastroscopy: an ulcer in the gastric antrum and a submucosal lesion in the fundus	Gastric fundus	54	4	Gastric antrum	Moderately differentiated adenocarcinoma	T1bN1M0/I b	Total gastrectomy	No	25	Alive without disease

<sup>1</sup>The tumor stage was defined according to AJCC TNM staging of tumors (7th edition, 2010).



**Figure 1.** Concurrent retroperitoneal GIST and gastric cancer. CT revealed a giant retroperitoneal mass (arrow head) and gastric wall thickening (arrow).

## Methods

We retrospectively reviewed all of the primary GIST cases that were diagnosed and surgically resected at our hospital between January 2005 and July 2014. Cases accompanying a synchronous primary digestive tract carcinoma were identified and included in this study. In total, 585 patients diagnosed with GIST in our hospital were evaluated. Thirty-two (5.5%) had a concurrent primary digestive tract carcinoma, including 19 (59.4%) men and 13 (40.6%) women. The median age was 64 years (range, 43-84). The reviewed data included age, sex, GIST location, size (maximum tumor diameter), mitotic index, immunohistochemistry data, characteristics of the digestive tract carcinoma and treatment results. The GIST risk group was classified according to the modified NIH criteria [12], and the carcinoma was staged using the American Joint Committee on Cancer (AJCC 2010, 7th edition) TNM staging system. Follow-up was conducted through the outpatient clinic or by telephone. The follow-up period was calculated from the date of surgery to the last follow-up or death. This retrospective study was approved by our institution's ethics committee.

All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 for Windows (IBM SPSS 21.0). Measurement data are expressed

as the mean  $\pm$  standard deviation or as the median (range). Differences between groups were analyzed using a two-tailed Student's t-test or the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical data. A *P* value of less than 0.05 was considered statistically significant.

## Results

### GIST characteristics

In 28 (87.5%) patients, GIST was incidentally detected during an operation intended for a carcinoma or microscopically found by pathologists during the surgical specimen evaluation. In the remaining 4 (12.5%) patients, the diagnoses were made preoperatively. In the intra- or postoperatively identified GIST subgroup (*n*=28), the GISTs were located in the stomach (*n*=21, 75.0%), small intestine (*n*=6, 21.4%) and duodenum (*n*=1, 3.6%). The tumor size varied from 2 to 35 mm (median, 8 mm). Moreover, the tumor size in 23 (82.2%) patients was less than 10 mm (microGIST). Twenty-five (89.3%) GISTs were classified as very low risk, and 3 (10.7%) were classified as low risk.

Four (12.5%) patients were included in the preoperatively identified GIST subgroup. Patient data are listed in **Table 1**. CT revealed both the GIST and carcinoma in patient 1 (**Figure 1**). Three of the GISTs arose from the stomach, and one arose from the retroperitoneum. The median size was 59.5 mm (range, 30-120). The mitotic index ranged from 4 to 12 mitotic figures per 50 HPFs (median, 5). Three GISTs were classified as intermediate risk, and one was classified as high risk. Compared to the intra- or postoperatively identified GIST subgroup, the preoperatively identified GIST subgroup showed a significantly larger tumor size, more mitotic figures and a higher risk grade, as presented in **Table 2**.

Histology revealed that all the GISTs had a spindle-cell growth pattern. In the immunohisto-

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**Table 2.** Comparison of GIST characteristics between the intra- or postoperatively identified and preoperatively identified GIST subgroups

Variables	Intra- or postoperatively identified GISTs	Preoperatively identified GISTs	P value
Age (years)	64.3±10.3	66.3±4.0	0.72 <sup>1</sup>
Sex (male/female)	18/10	1/3	0.28 <sup>2</sup>
Tumor size (mm)	8 (range, 2-35)	59.5 (range, 30-120)	<0.001 <sup>3</sup>
Mitotic figures (per 50 HPFs)	1 (range, 0-4)	5 (range, 4-12)	<0.001 <sup>3</sup>
Risk group			<0.001 <sup>2</sup>
Very low and low	28	0	
Intermediate and high	0	4	

<sup>1</sup>Student's t-test. <sup>2</sup>Fisher's exact test. <sup>3</sup>Man-Whitney U test.

chemical analysis, 96.9% (31/32) of the GISTs showed positive immunostaining for CD117, 90.6% (29/32) were positive for CD34, 100% (15/15) were positive for DOG-1, 31.0% (9/29) were positive for  $\alpha$ -SMA, and none were positive for S-100. The KIT mutational status was available for 2 cases, and mutations in exon 11 of KIT were detected in both.

### *Carcinoma characteristics*

Among the concurrent carcinomas, the primary sites involved were the stomach (n=24), esophagus (n=5), duodenum (n=2) and colon (n=1). Specifically, for the gastric cancer cases, 8 were located in the cardia, 2 were in the fundus, 7 were in the body, 5 were in the antrum, and 2 were in the pylorus. The histologic subtypes of gastric carcinoma included adenocarcinoma (n=21), signet ring cell carcinoma (n=2), and small cell neuroendocrine carcinoma (n=1). All the esophageal cancers were squamous cell carcinoma. Two duodenal carcinomas and 1 colon carcinoma were classified as adenocarcinoma.

The GIST and the concurrent carcinoma involved the same organ in 19 (59.4%) patients, including the stomach (n=18) and duodenum (n=1). In the other 13 (40.6%) cases, different parts of the alimentary tract were affected, such as gastric GIST with concurrent esophageal cancer (n=5), small intestinal GIST with gastric cancer (n=5), gastric GIST with colon cancer (n=1), retroperitoneal GIST with gastric cancer (n=1), and small intestine GIST with duodenal carcinoma (n=1).

### *Treatments and outcomes*

All the patients underwent radical surgery for the carcinoma and complete resection (R0) for

the GIST simultaneously. GISTs were removed en-bloc with the carcinoma, or a separate resection was performed when the GIST was located distal to the carcinoma. Laparoscopic surgery was performed in 5 patients. There was no perioperative mortality, but postoperative efferent loop obstruction and wound disruption occurred in the patient who received a pancreaticoduodenectomy. Two patients were treated with adjuvant imatinib (Gleevec, Novartis) for one year after surgery (400 mg daily).

With a median follow-up of 32 months (range, 9-80), 24 patients were alive without any sign of tumor recurrence or metastatic involvement. Seven patients in the series died: 6 died of carcinoma progression, and 1 died as a result of an accident. In the intra- or postoperatively identified GIST subgroup, no specific GIST progression was detected. In the preoperatively identified GIST subgroup, one patient was found to have liver metastasis 6 months after surgery. This patient received imatinib (400 mg daily), and a partial response was noted.

### **Discussion**

The coexistence of GIST and other tumors is an unusual event, and few published studies have focused on this topic. The reported proportion of additional primary tumors among GIST patients has varied from 2.95% to 33% in different studies [10, 11, 13-15]. In elderly patients, the rate is even higher, reaching 37.89% [16]. Previously, a large meta-analysis reviewed the literature and the cases reported therein and demonstrated that a second primary cancer occurred in 9.2% of GIST patients. Among the carcinomas, those of gastrointestinal origin predominated, reaching an incidence

of 4.7% (228/4,813) among GIST patients [11]. In agreement with previous studies, we found that 32 of 587 (5.5%) GIST patients developed a concurrent digestive tract carcinoma and that gastric adenocarcinoma was the most common [10]. However, the actual incidence is difficult to assess based solely on surgically resected specimens. Furthermore, GISTs smaller than 5 mm are likely to be missed by pathologists; in our series, only 4 GISTs were smaller than 5 mm.

In our study, microGISTs with a very low risk of progression accounted for the majority of the GIST cases. The most common location was the stomach. An increasing body of evidence has suggested that a microGIST is a common occurrence in the esophagogastric junction (EGJ) and stomach. An examination of 150 esophagogastric resections for esophageal or EGJ carcinomas identified GISTs smaller than 6 mm in 10% of the specimens [17]. MicroGISTs were also detected in 35% of surgically resected stomachs using whole organ sectioning [18]. However, small GISTs are thought to have an almost uniformly benign biological behavior, as there was no tumor-specific mortality among the 116 patients with lesions <2 cm in Mittinen's large series of GIST patients [6]. In our series, none of the microGISTs showed any evidence of progression, reflecting their relatively benign nature.

The etiology underlying concurrent GIST and gastrointestinal carcinoma remains obscure. Though GIST does coexist with other primary tumors in certain syndromes, such as Carney triad syndrome and neurofibromatosis type I, no specific links have been demonstrated between GIST and digestive tract carcinoma [19, 20]. Although the synchronous occurrence of GIST and other digestive tract carcinomas seems to be a coincidence, some researchers have hypothesized that unknown carcinogens induce the simultaneous proliferation and oncogenesis of epithelial and stromal cells. In fact, experimental studies showed that in rats, nitrosoguanidine combined with aspirin induced the joint development of leiomyosarcoma and gastric adenocarcinomas [21, 22]. Other tumors, including papillary renal cell carcinoma and myeloid leukemia, have been reported to have a nonrandom association with

GIST [23, 24]. While our results did not show any evidence of a specific link, more studies are warranted to clarify any potential relationship between GIST and additional gastrointestinal carcinomas.

Concurrent GIST and digestive tract carcinoma poses unique challenges for the proper clinical diagnosis and management of such patients. In our series, only 4 of the 32 patients (12.5%) found to have GIST with concurrent digestive tract carcinoma were diagnosed preoperatively. In another report, the proportion was 4.92% [16]. Considering the high incidence of microGISTs, endoscopic ultrasound may be helpful in diagnosing additional cases of GIST among digestive tract carcinoma patients. GISTs found during surgery may be mistaken as lymph node metastases and may thus affect therapeutic decisions [25]. Clinicians should be aware of the high possibility of this situation. Surgical resection is currently the only curative treatment for GISTs. To manage concurrent GIST and carcinoma, en-bloc resection of the GIST and carcinoma (if possible) or an additional complete resection of the GIST has been recommended by surgeons [26]. One concern is that residual GIST may progress to invasive disease because of the imprecise prediction of malignant potential based on gross appearance. Furthermore, residual lesions may be mistaken as evidence of relapse or metastasis of a previously removed malignancy [26].

Carcinoma seemed to have a greater unfavorable effect than GISTs on prognosis in our series. In the intra- or postoperatively identified subgroup, GISTs fell into the very low or low risk group, and no recurrences or metastases occurred; however, 6 patients died of carcinoma progression. In another study that included 42 patients with GIST and synchronous gastric cancer, the analysis showed that patient survival depended primarily on gastric cancer [27]. In elderly patients, overall survival primarily depends on synchronous digestive tract malignancies, mitotic count and co-morbidities [16]. One point highlighted by our study is that preoperatively identified GISTs showed more aggressive behavior, and thus, they may greatly influence prognosis. The clinical features of preoperatively and postoperatively identified GIST differed in tumor size, mitotic activity and risk



grade. However, a definitive conclusion could not be drawn because of the limited sample size and the retrospective nature of our study.

In conclusion, we discovered that 5.5% of GIST patients presented with a concurrent digestive tract carcinoma in a series of 585 GIST cases. The majority of GISTs are incidentally detected microGISTs, and gastric adenocarcinoma is the most common type of carcinoma. The en-bloc resection of both tumors or an additional resection is the treatment of choice. Carcinoma seems to have a greater unfavorable effect on prognosis than concurrent GIST. However, for preoperatively identified GISTs with a high risk of progression, adjuvant therapy is warranted.

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## Disclosure of conflict of interest

None.

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