Synchronous and metachronous neoplasms of different histogenesis with gastrointestinal stromal tumor (GIST):

10 years experience of a single institution.

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Synchronous and metachronous neoplasms of different histogenesis with gastrointestinal stromal tumor (GIST): 10 years experience of a single institution.

AIM: *Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal neoplasms of the gastrointestinal tract. Significant advances have been made in its pathogenesis, diagnosis, and treatment over the past few decades. However, little is known about the occurrence of synchronous or methacronous tumors with other histogenesis in addition to GISTs. The aim of this study was to present a series of 15 patients diagnosed with a second primary neoplasm in addition to GIST.*
MATERIAL AND METHODS: *Patients who were diagnosed with both GIST and other primary neoplasm between January 2010 and December 2019 were included in the study. Demographic, clinicopathologic and immunohistochemical parameters of the patients were analyzed along with the follow-up results*
RESULTS: *This study included 12 men and 3 women with a median age of 68 years (range: 57-83 years). Of the GISTs, 93.3% were localized in the stomach and 73.3% were at very low / low risk category. Of the second primary tumors, 66.6% were in the gastrointestinal tract. Detection of the GIST was synchronous in 9 cases, metachronous in 2 cases and preceded the GIST diagnosis in 4 cases. GIST was incidentally found intra-operatively in 3 of the cases. The mean size of the synchronous GISTs was 20 mm while the most common GIST-associated malignancy was gastric adenocarcinoma. The median follow-up times was 62 months (range: 13-129 months).*
CONCLUSIONS: *The prevalence of secondary malignancies in GIST patients is significantly higher than the healthy population. The high occurrence rate of additional primary tumors in GIST patients has focused the attention of surgeons on this problem. While it is not yet clear if there is a causal association or a common genetic mechanism for the concomitant occurrence of GIST with other malignancies, a closer surveillance of GIST patients is needed due to their proved increased prevalence of a second primary tumor especially during the first year after diagnosis.*

KEY WORDS: Gastrointestinal stromal tumor, Coexistence, Synchronous malignancy, Second neoplasm, Gastric adenocarcinoma

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common non-epithelial tumor of the gastrointestinal tract [1]. GISTs are the mesenchymal tumors which are originated from the interstitial Cajal cells localized on the gastrointestinal wall and from neoplastic transformation of Cajal cell progenitors [2]. The most common localization of GISTs is the stomach (50%-60%), followed by the small intestine (30%-35%), colon-rectum (5%) and esophagus (< 1%) [3,4]. GISTs usually develop in submucosal sites, but they can also develop as extra-luminal masses. Other sites such as omentum, mesentery and retroperitoneum (< 5% of total GISTs) are classified as extra-gastrointestinal [5,6].

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GISTs can be diagnosed with immunohistochemical staining methods by the extracellular membrane protein CD34, the tyrosine kinase receptor CD117 (KIT), and DOG1 protein.

The underlying pathophysiology in terms of molecular carcinogenesis mechanisms is the excessive increase in the function of the tyrosine kinase receptor (KIT) in the cell membrane. Platelet-derived growth factor receptor-alpha (PDGFR-α) is another oncogene responsible for the activation of the intracellular phosphorylation cascade. PDGFR-α mutated GISTs are generally seen in KIT positive tumors [7].

GISTs are generally seen after the age of 40, and they occur most commonly in the 60s.

The clinical symptoms depend mainly on the tumor diameter and the localisation. GISTs occasionally represent incidental findings either during surgery, at autopsy or during other interventional procedures for irrelevant diseases. Approximately 50% of the GISTs have already had distant metastasis when they are diagnosed, with the liver and peritoneum being the most common regions for metastasis.

Surgical intervention is the main method for histopathological diagnosis of GISTs. The primary purpose of surgical treatment in surgically resectable GISTs is to perform a resection
with clear surgical margins, leaving no visible tumor. Adjuvant treatment with a competitive inhibitor of tyrosine kinase, imatinib mesylate, is recommended in patients with a intermediate or high risk of recurrence and in tumors with a KIT or PDGFR-α mutation. A majority of patients respond to imatinib mesylate or achieve durable tumor growth stabilisation allowing a R0-resection, but some initially responsive patients experience tumor progress because of secondary drug resistance [8].

In addition to all these basics, there are very few data on the occurrence of secondary tumors with different histogenesis that develop synchronously or asynchronously in addition to GISTs. However, a second malignant tumor can significantly affect a patient's life expectancy and the treatment strategy designed by the oncologist.

Although some studies have published the relatively common synchronous or asynchronous coexistence of GIST with other malignant neoplasms, little is still known on the significance and prognostic impact of their association with other tumors of different anatomic localisation and histogenetic derivation. Today, the coexistence of GISTs with other malignancies is more often detected. Most of the cases have been documented as single case reports but several case series and reviews also exist on this issue [9].

The aim of this study is to review the clinical and pathological features of GISTs occurring with other malignancies in order to better understand this underestimated and not well-studied problem.

Material and Methods

Patients, Malignancies and Follow Up

We analyzed the clinical and pathological data of 141 consecutive patients with a confirmed diagnosis of GIST either in the pre-operative period or incidentally detected during examination of the resected gastrointestinal surgical specimens between January 2010 and December 2019. The analysis encompassed those patients, who were identified with another type of benign or malignant neoplasia. Among 141 GIST patients, we found 15 patients with a history of other primary neoplasms (10.6%). The time point of GIST diagnosis with regard to the diagnosis of the other malignancies was defined as either synchronous (during staging or surgical therapy of the diagnosed cancer) or non-synchronous (before the diagnosis of the other-type of cancer or after its treatment). GIST diagnosis was verified according to current diagnostic criteria. All tumors were examined histopathologically with preparations stained with hematoxylin and eosin. Immunohistochemical markers studied were CD34, CD117, DOG-1, smooth muscle actin (SMA), desmin and S-100. Ki-67 index and mitosis numbers were calculated. Mitoses were counted in 50 high-power fields (HPFs). One HPF corresponded to an area of 0.238 mm^2. The risk category was defined by assessing the tumor size and mitotic count following the consensus guidelines of the National Institutes of Health-(NIH-NCI) workshop and the Miettinen's criteria [10-12]. Before the operation, thoraco-abdominal computed tomography and upper gastrointestinal endoscopy and/or endosonography were performed in all patients. The type of surgery was decided according to the location and size of the lesion.

Neurofibromatosis type 1 (NF-1) and Carney triad-associated tumors or familial GIST were excluded from this study. Clinical and histopathological records were reviewed. Patient's age, sex, tumor localization, malignant potential (risk classification) and selected immunohistochemical parameters were assessed. The median follow up of patients was 62 months (range: 13-129 months).

The informed consent was read and signed by all participants. This study was approved by the Institutional Review Board of our institute (IRB No. 40525243/20.03.2020/4). All procedures performed in this study involving human participant were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA).

Table I - *Risk predicition according to size, site and mitotic index (from Fletcher et al. 12)*

Size	Mitotic count	Stomach	Jejunum	Risk
< 2 cm	< 5 / 50 HPF	7	0	Very low
2-5 cm	< 5 / 50 HPF	4	0	Low
< 5 cm	6-10 / 50 HPF	0	0	Intermediate
5-10 cm	< 5 / 50 HPF	1	1	Intermediate
> 5 cm	> 5 / 50 HPF	1	0	High
> 10 cm	Any mitotic rate	0	0	High
Any size	> 10 / 50 HPF	1	0	High

Continuous data were presented as mean (standard deviation) or median (range), and categorical data as frequency. Student's *t*-test was used for comparison of continuous variables. Shapiro-Wilk normality test was performed for numerical variables such as age, tumor size and follow-up time. Student's *t*-test was used to analyze the relationship between tumor size and mortality and recurrence. Based on the results of analyses, the *p* value < 0.05 was considered to be statistically significant.

Results

Risk Classification

GISTs were divided into four risk groups based on a risk assessment table based on broad pathological consensus published by Fletcher in 2002 using mitotic activity (number of mitoses / 50 HPFs, 400x magnification field of view) and tumor size (maximum diameter) as the two most important prognostic parameters: very low risk, low risk, intermediate risk, and high risk tumors (Table I) [12]. Based on the risk groups, the tumor diameter was <5 cm and the number of mitotic figures < 5/50 HPFs and therefore they were classified as very low risk in 7 cases and low risk in 4 cases. Two GIST cases, the gastric GIST with a diameter of 9 cm and a mitotic index of 1-2/50 HPFs and the jejunal GIST with a diameter of 8 cm and a mitotic index of <5/50 HPFs, were classified as intermediate risk. The last two cases of GIST whose tumor size was 10 cm and mitotic index was 5-6/50 HPFs and whose tumor size was 5 cm and mitotic index was 11/50 HPFs were classified as high risk.

Demographic and Clinicopathologic Characteristics

In 15 of the 141 consecutive cases, the occurrence of a synchronous or asynchronous second tumor was observed. Among the 15 GISTs, 14 were gastric origin (93.3%), and one was found in the small intestine (6.7%), The mean age was 68 years (range: 57–83 years). The male / female ratio is 12/3 (80% / 20%). Two cases had multi-regional multiple tumors, and 11 developed either synchronous (9 cases) or metachronous (2 cases) tumors with different histogenesis. The clinical features of the fifteen patients are briefly summarized in Table II.

Associated neoplasms

Secondary neoplasms associated with GISTs were squamous cell carcinoma of lung, non-Hodgkin lymphoma, and adenomatous hyperplasia of the left adrenal gland

Table II - *Patient characteristics, features of GIST and associated malignancies*

Case	Sex	Age	Site (GIST)	GIST Diagnosis	GIST-associated neoplasm (Tumor Localisation)	GIST-associated neoplasm (Tumor Type)
1	M	76	Stomach	6 years later	1-Lung 2-Bone marrow 3-Left adrenal gland	1-Squamous cell carcinoma 2-Non-Hodgkin lymphoma 3-Adenomatous hyperplasia
2	M	62	Stomach	18 months earlier	1-Right adrenal gland 2-Esophagus and Stomach	1-Pleomorphic sarcoma 2-Double Leiomyomas
3	M	61	Stomach	Simultaneous	Gallbladder	Adenocarcinoma
4	F	61	Stomach	Simultaneous	Ovary	Serous adenocarcinoma
5	M	71	Stomach	4 months earlier	Bladder	Transitional cell carcinoma
6	F	68	Jejunum	8 years earlier	Sigmoid colon	Low grade musinous neoplasm
7	M	66	Stomach	Simultaneous	Left aderanl gland	Pheochromocytoma
8	M	83	Stomach	Simultaneous	Stomach	Adenocarcinoma
9	F	70	Stomach	Simultaneous	Stomach	Adenocarcinoma
10	M	70	Stomach	5 months earlier	Renal pelvis	Papillary urothelial carcinoma
11	M	65	Stomach	2 years later	Liver	Hepatocellular carcinoma
12	M	57	Stomach	Simultaneous	Stomach	Adenocarcinoma
13	M	77	Stomach	Simultaneous	Remnant stomach	Adenocarcinoma
14	M	67	Stomach	Simultaneous	Stomach	Adenocarcinoma
15	M	75	Stomach	Simultaneous	1-Esophagus 2-Esophagogastric junction	1-Epidermoid carcinoma 2-Double Leiomyomas

in 1 case, leiomyomas of esophagus and stomach, and pleomorphic sarcoma of the right adrenal gland in 1 case, gallbladder adenocarcinoma in 1 case, ovarian serous adenocarcinoma in 1 case, transitional cell carcinoma of bladder in 1 case, low grade mucinous neoplasm of sigmoid colon in 1 case, pheochromocytoma of the left adrenal gland in 1 case, papillary urothelial carcinoma high grade of renal pelvis in 1 case, hepatocellular carcinoma in 1 case, esophageal epidermoid carcinoma and leiomyomas of esophagogastric junction in 1 case and gastric adenocarcinoma in 5 cases. In 9 of 15 patients, the tumor association was synchronous and in 2 patients metachronous. The most important data are summarized in Table II.

Synchronousity

In nine patients (60%), detection of the GIST and the second tumor was simultaneous. In two patients, there were more than one non-GIST tumors either preceding (n = 1) or following (n = 1) the diagnosis of GIST. The mean time interval between previous additional malignancy and GIST was 24.6 months (range: 5 - 96 months). In five patients (33.3%) GIST was found during follow-up for a known other malignancy and in two patients (13.3%), the second malignancy was detected after the diagnosis of GIST. In one patient, two separate non-GIST neoplasms were found in the esophagogastric junction. The chronology of GIST diagnosis is detailed in Table II either during the diagnostic procedures for other tumors (5 cases, 33.3%) or during surgery (3 cases, 20%).

Incidentality

A GIST was an incidental finding, that is, an incidentaloma in 8 cases (8/15, 53.3%): the GIST was detected incidentally either during abdominal surgery for other reasons in 3 cases (3/15, 20%) or on the examination of the resected specimen in 5 cases (5/15, 33.3%). The incidentality of GIST diagnosis is presented in Table III. In the first case, cholecystectomy with resection of gallbladder bed for gallbladder adenocarcinoma was performed, and a gastric GIST upon intra-operative inspection of abdominal cavity was detected, which was treated by a gastric wedge resection. In the second case, total abdominal hysterectomy with bilateral salpingo-oophorectomy followed by bilateral pelvic and paraaortic lymphadenectomy was performed for ovarian cancer, and a gastric wedge resection was also performed for incidentally discovered gastic GIST during laparotomy. In the third case, transhiatal esophagectomy was performed for the epidermoid carcinoma of esophagus, and a gastric GIST was recognized on the body of stomach on the exploration of the abdomen which was removed by a gastric wedge resection. In other 5 cases (5/15, 33.3%) who underwent total gastrectomy due to primary gastric adenocarcinoma, the definitive histological examination revealed a concomitant small gastric GIST in all of 5 patients on the examination of the resected specimen.

Surgical treatment

The majority of patients (14/15, 93.3%) underwent open surgery, and one patient (6.7%) underwent laparoscopic excision. Types of surgery performed are showed in Table III. Fourteen tumors (93.3%) were completely resected (R0) and one was not resectable due to infiltration into small bowel mesentery at the ligament of Treitz. This patient received a gastroenterostomy for unresectable jejunal GIST, and was diagnosed with a low grade *mucinous neoplasm of sigmoid colon eight years later.*

Follow-Up and Disease Outcome

Duration of follow-up varied between 13 and 129 months with a mean follow-up of 62 months (Table III). Currently, one-third of patients (n = 5, 33.3%) are alive. No recurrences or metastases from GIST were detected on last follow-up. There was only one mortality due to multi-organ failure in the immediate postoperative day 1 in a patient who underwent total gastrectomy for a perforated gastric adenocarcinoma in the emergency setting. During the 10-year follow-up period, 9 patients (60%) died of recurrence or distant metastasis of the associated other malignancy. No patient died of GIST. Five patients (33.3%) had no recurrence. A margin-negative R0 resection was accomplished in all resective procedures. In 9 patients with synchronous tumors, the resection of GIST and the second tumor was performed in one single surgery time. After surgery, 11 patients (73.3%) received no treatment for a very low / low risk of recurrence according to classification criteria, and a precautionary treatment with imatinib mesylate has been administered to four patients.

Histopathological Features

The mean tumor diameter was 3.3 cm and the largest tumor diameter was 10 cm in GIST patients. The surgical margin was negative in all patients. CD34 and CD117 stained positive with immunohistochemical method. The findings were consistent with a GIST. c-KIT (CD117) was positive in 14/15 cases (93.3%), CD34 was positive in 13/14 cases (92.8%), SMA was positive in 13/14 cases (92.8%), S100 was positive in 7/13 cases (53.8%), DOG1 was positive in 8/8 cases (100%), and desmin was negative in 9/9 cases (100%).

TABLE III - *Incidentality of GIST diagnosis, types of surgery and survival of patients*

Case	Incidentality(GIST)	Surgery	Survival
1	No	Laparoscopic gastric wedge resection	Alive (23 months)
2	No	Gastric wedge resection +Distal esophagectomy	Exitus (117 months)
3	Yes/Intra-operatively	Gastric wedge resection + Cholecystectomy	Alive (118.5 months)
4	Yes/Intra-operatively	Gastric wedge resection + TAH+BSO+BPPLND	Exitus (50.5 months)
5	No	Gastric wedge resection	Alive (125.5 months)
6	No	Gastroenterostomy(Unresectable jejunal GIST)	Alive (129 months)
7	No	Total gastrectomy	Alive (34 months)
8	Yes/Pathologically	Total gastrectomy	Exitus (17 months)
9	Yes/ Pathologically	Total gastrectomy	Exitus (Early postoperative period)
10	No	Gastric wedge resection	Exitus (28 months)
11	No	Gastric wedge resection	Exitus (53 months)
12	Yes/ Pathologically	Total gastrectomy	Exitus (54 months)
13	Yes/ Pathologically	Total gastrectomy	Exitus (31.5 months)
14	Yes/ Pathologically	Total gastrectomy	Exitus (70 months)
15	Yes/ Intra-operatively	Gastric wedge resection + Transhiatal Esophagectomy	Exitus (13 months)

TAH: Total Abdominal Hysterectomy
BSO: Bilateral Salpingo-oophorectomy
BPPLND: Bilateral pelvic and para-aortic lymph node dissection

TABLE IV - *Histopathological and immunohistochemical characteristics of GIST patients*

Case	Size (GIST)	Mitotic Index (x/50 HPFs)	Ki67	CD117	CD34	Dog1	SMA	Desmin	S100
1	3 cm	1	<1%	+	+	+	Focally +	-	NA
2	1 cm	<5	<1%	-	+	NA	-	-	Focally +
3	2-3 cm	2-3	1-2%	+	+	NA	Focally +	-	Focally +
4	2 cm	<5	<1%	+	+	NA	Focally +	NA	Focally +
5	4 cm	1-2	1-2%	+	+	NA	Focally +	-	Focally +
6	8 cm	<5	1%	+	-	NA	Focally +	-	+
7	10 cm	5-6	6-8%	+	+	+	NA	NA	-
8	1.1 cm	2	1-2%	+	+	+	Focally +	-	-
9	1 cm	1-2	<1%	+	+	NA	Focally +	NA	-
10	5 cm	11	5%	+	+	+	Focally +	-	-
11	9 cm	1-2	<1%	+	+	+	Focally +	-	-
12	0.5 cm	0	<1%	+	+	+	Focally +	-	NA
13	0.5 cm	0	<1%	+	+	+	Focally +	NA	Focally +
14	0.3 cm	<1	<1%	+	NA	+	Focally +	NA	Focally +
15	0.7 cm	1	<1%	+	+	NA	Focally +	NA	-

HPF: High Power Field, NA: Not Applicable

The Ki-67 index was 6-8% in one patient and 1-2% in other patients. Necrosis was observed in a gastric GIST in a patient with pheochromocytoma. Histopathological and immunohistochemical characteristics are given in Table IV.

Discussion

There is a continuously increasing knowledge about presentation of GIST with other primary tumors of different histogenesis. The synchronous, metachronous or antecedent occurrence of GISTs in patients with a recent or remote history of cancer represents a special and challenging situation to surgeons, oncologists and pathologists. Until today no underlying connections have been found between GISTs and intra-abdominal malignancies. Such occurrence has been mainly described in the literature in the form of case reports and rarely of case series which has not been sufficient to prove if there is any association between these two entities.

A variety of hypotheses attempt to explain the synchronous existence of GISTs with other primary neoplasms. These hypotheses include the relations to genetic predisposition, environmental risk factors, mutagenic effect from previous radiation or chemotherapy, Helicobacter

pylori infection, chronic atrophic gastritis, and coincidental findings [13-16]. Currently, there are 3 theories that describe the pathogenetic mechanisms underlying the occurrence of synchronous GIST-associated tumors. The first hypothesis is an incidental, non-causal relationship between GIST and other malignancies, suggesting that two or more tumors occur together incidentally [17]. Simple coincidence could be the case, especially in centres having high incidence rates of gastric surgery [16,18]. The second model is that exposure to potential carcinogens can trigger oncogenetic pathways in both epithelial and mesenchymal cells [19,20]. Maiorana *et al*. suggested that a single carcinogenic agent might interact with 2 neighboring tissues, inducing development of tumors of different histotypes in the same organ [16]. The third hypothesis, genetic mutations in both epithelial and stromal cells, are hypothesized to be the cause of the synchronous tumor occurrence. Today there is no conclusive evidence to support this theory [21,22].

There have been many reports of additional malignancies in patients diagnosed with a GIST. In 2000, at the first time Maiorana *et al*. reported on a small series of epithelioid gastric GIST associated with additional neoplasms [16]. In the literature, the reported frequency of additional neoplasms in GIST patients varies by 4.5% to 33%. A review of the literature and own cases by Agaimy *et al*. revealed 518 cancers in 486 GIST patients among a total of 4813 patients, accounting for secondary neoplasias in 10.1% of GIST patients [9]. Ruka *et al*. reported on 18 patients (10.0%) with a history of other malignancies among 180 GIST patients with a median age of 60 years whereby two GIST patients suffered from more than one other tumor [23]. In our study, most of the patients were men (80%), and the average age was 68 years (range: 57–83 years). The association between GIST and second primary tumor was 10.6%, similar to the values reported in the literature. Our data are also supported by observation of Chacon *et al*. on smaller cohort of GIST patients, who found also approximately 10% GIST patients with prior history of other solid cancer [24].

GIST patients have a 44% increased prevalence of cancer occurring before and a 66% increased relative risk after the GIST diagnosis [25]. The maximum increase occurs within the first year before and after the GIST diagnosis, suggesting a much closer surveillance of GIST patients versus the general population. In a meta-analysis in which 19,627 GIST patients were evaluated, secondary tumors were found to be synchronous in 14%, metachronous in 3%, and pre-GIST in 4.6% [26].

Waidhauser *et al*. evaluated 22 studies involving 12,050 GIST patients, and found that 50% of the second neoplasms accompanying GIST (n = 2426) occurred concurrently with GIST, 26% occurred before GIST, and 24% were diagnosed after GIST [27]. They determined that GISTs are most frequently synchronously observed in intra-abdominal malignancies. In our study, second primary tumor was diagnosed before GIST in 26.6% of the patients. However, it was synchronous with GIST in 60% of the cases, and was diagnosed after GIST diagnosis in 13.3% of our patients. Hence, in our study, second primary tumor was more common synchronous with GIST diagnosis. This frequently encountered synchronous coexistence is similar to that reported in the literature.

Time intervals for the emergence of GISTs and secondary tumors vary in the literature. The meticulous follow-up of patients after GIST diagnosis is extremely important Mayr *et al*. found that when GIST was diagnosed after secondary malignancy, the median time interval was 50 months [28]. If secondary malignancy was diagnosed after GIST, the median time interval was 29 months. Murphy *et al*. reported that the median delay from initial cancer diagnosis to GIST diagnosis was 3.6 years for all patients, and the median time from GIST diagnosis to cancer diagnosis was 10 months for the entire cohort [29]. In our study, the median time between the two tumors in patients diagnosed with second primary tumor before GIST diagnosis (n = 4) was 31 months (4–96 months). The median time between two tumors in patients diagnosed with second primary tumor after GIST (n = 2) was 48 months (range: 24–72 months). Considering the number of patients and follow-up periods, there were differences between the timing of diagnosis of two tumors in our study. If the time interval for second primary tumor development after GIST is short, then patients should be followed up closely, and screening tests should be performed accordingly.

The size of GISTs simultaneously resected with other malignancies tended to be smaller and very low or low risk of malignant potential [30]. Small GISTs (<2 cm) may be asymptomatic and non-malignant when diagnosed but have a potential for malignant transformation. In the present study, there were three patients with intermediate/high risk in the non-synchronous group, and they might more likely to experience tumor progression than that of patients with very low/low risk. The tumor size of GISTs synchronous with other malignancies is usually smaller than 2.0 cm [9,22,31-35], and only few patients (16.7%) present a tumor size > 2.0 cm [33]. Similar to these reports, patients in the synchronous group in the present series was small with a median size of 2 cm. In addition, two (13.3%) patients demonstrated a tumor size ≥ 2 cm.

Subclinical microscopic gastric GISTs have been reported in the recent years. Kawanowa *et al*. reported that the incidence of asymptomatic microscopic GIST in stomachs resected for gastric carcinoma was 35% [25]. Agaimy *et al*. found that microscopic gastric GISTs presented in 22.5 % of patients aged 50 years old or older through a series of consecutive autopsies, and reported that the "*microscopic*" gastric GISTs in autopsy specimens measured 2-10 mm in size (mean: 5 mm) [9]. In

a retrospective study of 207 patients who underwent gastrectomy or esophagectomy for non-GIST neoplasms, Chan *et al.* found that 15 synchronous GISTs in the upper gastrointestinal tract of 11 (5.3 %) patients were found with an average size of 0.5 cm (0.1-4.0 cm) [36]. In our study, four (26.6%) patients demonstrated a median size of 5 mm (0.3-0.7 cm) of microscopic GISTs concomitant with esophageal and gastric adenocarcinoma.

GISTs are usually identified incidentally during surgeries or by postmortem examination in 15% to 30% of cases [37]. Miettinen *et al.* showed that the GISTs were detected incidentally during abdominal surgery or a medical procedure for gallbladder disease in 2.4 % and colorectal carcinomas or adenoma in 1.6 % of the cases in 1765 gastric GISTs [10]. In our study, three GISTs (20%) were accidentally discovered during the surgical exploration of the other conditions and five GISTs (33.3%) were incidentally found on the examination of the resected specimen. However, seven GISTs (46.7 %) were identified during preoperative examination. A careful exploration for synchronous GISTs should be carried out during gastrointestinal cancer surgeries. Since most of the incidental GISTs were less than 1 cm in diameter, serial sections skipping a depth greater than 1 cm could leave these tumors undetected. Thus, the detection rate greatly depends on the number of histological sections per specimen examined.

The most frequent types of GIST-associated cancers are gastrointestinal carcinomas (47%), lymphoma/leukemia, (7%), carcinomas of prostate (9%), breast (7%), kidney (6%), lung (5%), female genital tract (5%), carcinoid tumors (3%), soft tissue and bone sarcomas (3%), malignant melanoma (2%), and seminoma (1%) [9,14,16,38]. Gastric adenocarcinoma is the most common malignancy associated with GIST [21]. GISTs were present with high frequency (35%) in the resected stomach of patients with gastric cancer [25]. In our study, adenocarcinoma was more frequent in cases of GISTs concomitant with a second neoplasia (77.7%) just as in other publications. According to our results and in concordance with the current literature, the most common GIST-associated neoplasms are reported to be adenocarcinomas of the gastrointestinal tract, comprising up to 38% of all the second primary malignant tumors found in patients with GISTs [21]. Gastrointestinal cancers constituted 60% (9/15) of the second primary tumors in our series.

GISTs should be excised when incidentally discovered during surgery for other malignancy and if needed targeted therapy with imatinib should be considered. Surgical exploration in these patients should be careful and comprehensive. Minimally invasive surgical procedures, such as endoscopic and laparoscopic resection, can safely be performed to decrease operative trauma especially in elderly patients. It has been recommended that incidental GISTs be removed en bloc with other tumors when possible. Alternatively, local resection should be performed [16,38,39]. The majority of patients (14/15, 93.3%) underwent open surgery, and one patient (6.7%) underwent laparoscopic excision We suggest that excision of incidental GISTs be carried out only if this additional resection does not compromise the integrity of the gastric conduit and the intestinal continuity.

Inhibitor of Growth 4 (ING4) is a novel tumor suppressor gene that is reported to be down-regulated in various tumors including GISTs originated from different locations. Recently, Sahin *et al.* reported that the low ING4 expression level was found to be related with unfavorable prognosis [40]. They suggested that loss of ING4 expression might play a role in the progression of GISTs and might be used as a potential prognostic tool. Besides, microsatellite instability (MSI) occurs in GISTs originating mainly in the stomach and more frequently related to hereditary syndromes, and in GISTs arising in patients with previous or concomitant neoplastic pathologies. In their series with 12 cases affected by GIST, 4 of whom had also a second tumor, Marino *et al.* evaluated all cases for Mismatch Repair System (MMR) with immunohistochemical technique MLH1/PMS2 and MSH2/MSH6 [41]. They demonstrated the expression of all proteins in the neoplastic cells, and no occurrence of MSI in their series of GISTs was noted. As a result, they suggested that the determination of MSI status would be a marker for new treatments and it can be a predictive indicator for selecting patients who can benefit from targeted therapy [42].

Synchronous GISTs that were incidentally found during the resection of other gastrointestinal neoplasms negatively affect long-term survival, although they often pose very low or low risk of malignant potential [36,43]. As expected, the duration of the follow-up time was closely linked to the occurrence of secondary malignancies in GIST. Rodriquenz *et al.* suggested that GIST could be considered as a "*sentinel tumor*" and surveillance not only for GIST but also for second malignancies is an important compound of the management of GIST patients, particularly in the first year after diagnosis [44]. The presence of an additional malignancy within 6 months of a GIST diagnosis is associated with poorer survival. In our study, 66% of our patients (10/15) died due to secondary tumors during the median follow-up of 62 months (13-129 months). We believe that the coexistence of other malignant tumors negatively influences the prognosis of patients with GIST.

The limitations of our study were its retrospective and single-centered nature, lack of mutation analysis in GISTs, and the small number of patients.

Conclusion

In conclusion, we have reported the occurrence of other type of neoplasms in 10.6% of patients with GIST at our institute, an incidence in line with the literature.

The concurrence of other tumors and GIST raises questions about a potential common origin and carcinogenetic mechanisms in these different tumor types thus deserving future studies. It seems that the prognosis in this subset of GIST patients is mainly determined by the other malignancy and not by GIST. Therefore treatment algorithms should focus on the prognostically relevant malignancy. Finally, a thorough intraoperative exploration of the abdominal cavity supplemented by awareness of GIST and their morphological and biological characteristics is mandatory for recognition of coincidental GIST and their correct interpretation. We suggest a regular and continuous follow-up of GIST patients at least for 10 years.

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