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Coexistence of gastrointestinal stromal tumors with other neoplasms

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Background. The purpose of this study was to assess the prevalence of other neoplasms in patients with gastrointestinal stromal tumors (GISTs) and to compare clinical and histopathological data in patients with a GIST and accompanying neoplasms and in patients with GIST only. ***Methods.*** The analysis encompassed 82 patients with a GIST from among 330300 patients whose surgical specimens, biopsies, and autopsies were evaluated between January 1989 and June 2006. A subgroup of patients with other types of neoplasms was selected. ***Results.*** Other neoplasms in patients with a GIST were diagnosed in 22 of the 82 (26.8%) patients. The most common accompanying neoplasms were colorectal (nine cases) and gastric (four cases) adenocarcinoma, as well as pancreatic adenocarcinoma (three cases). There was a tendency toward more common localization of a GIST in the small intestine in patients with other neoplasms than in patients with a GIST alone ($P < 0.09$). Tumors with very low risk of aggressive behavior were more frequent in patients with a GIST accompanied by other neoplasms than in the other group ($P < 0.05$). No phenotypic differences in GIST cells were found between the two groups. ***Conclusions.*** In almost 27% of the study population, GISTs coexisted with other neoplasms. A greater proportion of patients with a GIST localized in the small intestine and/or characterized by a very low risk of aggressive behavior and accompanying other neoplasms, compared with a GIST alone, most likely reflects the fact that in the first group, GISTs tended to be an incidental finding during surgery. The results were affected by patient selection and the type of tissue material available.

Key words: gastrointestinal stromal tumor, multiple neoplasms, synchronous neoplasm

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Introduction

Gastrointestinal stromal tumors (GISTs) are localized in the alimentary tract, omentum, mesentery, or retroperitoneum. They are the most common mesenchymal tumors of the alimentary tract and consist of spindle, epithelioid, or polymorphic cells. A mixed histological pattern is also common. The annual incidence of GISTs is 8–40 cases per one million people. The mean patient age is 55–65 years.[1–6] GISTs most likely derive from Cajal cells or related multipotential cells.[2,7] They usually show positive immunohistochemical reactivity with CD117 (c-kit) antibody.[1–3,6–8] The role of a mutation involving *C-KIT* and *PDGFRA* proto-oncogenes is well documented.[1–4,7–12] Imatinib mesylate is a competitive inhibitor of tyrosine kinases (BCR-ABL, ARG, KIT, PDGFRA, and PDGFRB), and plays an important role in the treatment of patients with GISTs.[3,4,7,11–13]

The most common localization of GISTs is the stomach, followed by the small intestine, rectum, esophagus, and other organs.[1–3,5,7,14] Approximately 20%–30% of GISTs are malignant;[1] however, at present every case of GIST is considered as potentially malignant.[3,8] Five-year survival following a complete resection is about 50%.[13]

In about 20% of cases, GISTs are an incidental finding at surgery, and in 10%, they are an incidental finding at autopsy.[4] Assessment of the incidence of GISTs is difficult because most of the epidemiological data is based on patients treated with surgery in reference centers, or the data do not comply with contemporary diagnostic criteria.[4–6,15]

Approximately 60%–80% of GISTs react positively to anti-CD34, 30%–40% of GISTs are SMA positive, and they rarely show a positive reaction to anti-desmin or anti-S100.[1,2,7,8] Tumor size and mitotic index are important risk factors of aggressive behavior. GISTs are qualified in four risk categories upon assessment of

these risk factors.[4,7,8] In population studies, the anatomic location did not have prognostic value.[4,5]

The morphological and molecular properties that differentiate GISTs from other tumors have been described recently. However, numerous aspects of their biology are unclear—especially diagnostic techniques and criteria, visualizing methods useful in the evaluation of tumor stage and monitoring of treatment, surgical treatment details, and the role of adjuvant and neoadjuvant therapy.[3]

Coexistence of a few primary dissimilar neoplasms in one patient is a rare phenomenon.[16] The problem of the coexistence of GISTs with other neoplasms is complex, since the tumors can develop synchronously or asynchronously. GISTs may be diagnosed before the diagnosis of another tumor, or may be found some time after. The GIST as well as the other neoplasm may be an incidental finding during visualization examinations or upon surgery.

Numerous synchronous and asynchronous cases of GIST and other neoplasms have been reported (Table 1). Notably, a group of researchers from Germany and the United States compared findings in the literature with their own large data set.[56] Of special interest are cases in which one or more tumors were found within the same organ.[18–22,28–30,44,46,55,56] Unfortunately, most reports present only single cases.[17–21,23,29,35,37–55]

The aim of the study was to (1) assess the prevalence of other neoplasms in patients with a GIST; (2) assess the most common tumor types and their localization in patients with a GIST; and (3) compare the basic clinical data and selected histopathological parameters in patients with a GIST and accompanying neoplasms with those in patients with a GIST only.

Table 1. Literature data on the accompanying neoplasms in patients with gastrointestinal stromal tumors

Tumor site or type	Reference Nos.
Gastric carcinoma	4, 17–30
Breast carcinoma	24, 28, 31, 32
Cervical carcinoma	24, 33
Endometrial carcinoma	24, 28
Ovarian carcinoma	28, 34
Lung carcinoma	24, 28
Colorectal carcinoma and adenoma	4, 14, 24–28, 31, 32, 33, 34, 35, 36
Pancreatic carcinoma	4, 28, 34
Hepatocellular carcinoma	37
Melanoma	26, 31, 38, 39
Prostatic carcinoma	28, 31, 32
Renal carcinoma	24, 28, 31, 32, 40, 41
Squamous cell carcinoma of the tonsil	34
Disseminated squamous cell carcinoma	26
Thyroid carcinoma	31
Gallbladder carcinoma	18
Carcinoma of the Vater's papilla	42, 43
Duodenal Brunner's gland adenoma	25
Esophageal carcinoma	32, 44
Cutaneous carcinoma	32
Seminoma	24
Granular cell tumor	17
Chronic lymphatic leukemia	24, 25
MALT-lymphoma	20, 45, 46
Non-Hodgkin lymphoma (not precisely specified)	34
Burkitt's lymphoma	47
Anaplastic lymphoma	26
High-grade follicle center lymphoma	28
Plasmocytoma	28, 34
Carcinoid	22, 24–27, 34, 48–50
Somatostatinoma	51
Pheochromocytoma	26
Neuroendocrine carcinoma	28, 52
Neuroblastoma	53
Osteosarcoma	24, 54
Uterine sarcoma	24
Lipoma	24, 55

MALT, mucosa-associated lymphoid tissue

Table 2. Characteristics of the center where the study was performed

Reference level	Third
Particular interest	Gastrointestinal pathology, hematopathology
Population inhabiting the area covered by the center	approx. 1 million
Number of pathologists	8
Structure of the main hospitals submitting specimens for examination	Two multiprofile hospitals of the third reference level for adult patients, one multidisciplinary children's hospital. Each hospital has approx. 15 000 admissions per year and approx. 50 000 walk-in patients; includes 3 surgical wards (one children's) and 2 gastroenterology wards (one children's)
Number of patients whose specimens were submitted to histopathological examination during the study period	330 300 (median, 17 500/year; range, 13 400–24 900)
Number of autopsies/year, median (range)	212 (105–274)
Number of surgical specimens/year, median (range)	
1. Esophagus	28 (10–62)
2. Stomach	75 (54–95)
3. Small intestine	34 (23–51)
4. Large intestine	227 (112–327)
5. Pancreas	47 (12–60)
Incidence of malignant neoplasms among the population covered by the study center and in Poland (2003), respectively	335/100 000 per year 317/100 000 per year
Mortality rate due to malignant neoplasms among the population covered by the study center and in Poland (2003), respectively	236/100 000 per year 231/100 000 per year
Five most common malignant neoplasms in men among the population covered by the study center	Carcinoma of lung, prostate, urinary bladder, stomach, and large intestine
Five most common malignant neoplasms in women among the population covered by the study center	Carcinoma of breast, lung, endometrium, cervix, and large intestine

Methods

This retrospective analysis encompassed 82 patients with a GIST from among 330 300 patients whose surgical specimens, biopsies, and autopsies were evaluated between January 1989 and June 2006 in the Department of Pathology, Medical University of Silesia, Katowice, Poland. Information on the center where the study was conducted as well on the background population is presented in Table 2. Unfortunately, precise data on the GIST incidence rate in Poland are not available. The only Polish study encompassing six diagnostic centers in Poland (excluding ours) found 200 cases of GIST during 1982–1999. In seven cases, GISTs coexisted with another neoplasm.[26]

During the study, an additional group of patients with another neoplasm was distinguished among patients with a GIST. We based our definition of GIST on that of Fletcher et al.[8] Patient age, sex, tumor localization, morphological variant (spindle-cell, epithelioid, mixed), malignant potential, and selected immunohistochemical parameters were assessed. Malignant potential was assessed by generally accepted criteria, including largest tumor dimension and mitotic rate (mitotic count per 50 high power fields).[7,8] In addition to assessment of CD117 in tumor cells, reactions with CD34, SMA, and S-100 proteins were also studied. Immunohistochemical examinations were performed on material fixed in buffered formalin and embedded in paraffin, with DAKO (Glostrup, Denmark) antibodies according to the manufacturer's guidelines.

Continuous variables were assessed with the Mann-Whitney U test, and categorical variables with the χ-squared test or χ-squared test with Yates correction for continuity. A P value of less than 0.05 was considered statistically significant.

Results

Eighty-two patients with GISTs were identified, including 38 (46.3%) men and 44 (53.7%) women. The most common localization of the GIST was the stomach (45, 54.9%) and small intestine (22, 26.8%). There were 26 (19 malignant and 7 benign) other neoplasms in patients with a GIST. These tumors were diagnosed in 22 of 82 [26.8%, 95% confidence interval (CI) 18.1%–37.2%] patients. Seventeen of 82 (20.7%) patients with a GIST had another malignant neoplasm. Three of 82 (3.7%) patients with a GIST had other malignant and benign neoplasms. Two of 82 (2.4%) patients with a GIST had a benign neoplasm. The most common neoplasms were adenocarcinoma of the colon or rectum (nine cases), adenocarcinoma of the stomach (four), and ductal adenocarcinoma of the pancreas (three). In 18 (81.81%) patients, the second tumor was synchronous with the

Table 3. Characteristics of patients with a gastrointestinal stromal tumor (GIST) and other tumors

Case No.	Sex	Age	GIST	Malignant potential	Other tumor	Other tumor localization	When
1	M	53	Stomach	Very low	Adenocarcinoma	Stomach	Simultaneously
2	M	63	Stomach	Low	Adenocarcinoma	Stomach	Simultaneously
3	F	65	Stomach	High	Adenocarcinoma	Colon	GIST 6 months later
4	F	56	Stomach	Very low	Adenocarcinoma	Colon	Simultaneously
5	M	66	Stomach	Intermediate	Adenocarcinoma	Colon	Simultaneously
6	M	77	Stomach	High	Adenocarcinoma Adenoma	Colon Hypophysis	Simultaneously
7	F	68	Stomach	Very low	Adenocarcinoma Tubular adenoma Leiomyomas	Colon	GIST 5 months earlier Simultaneously
8	F	39	Stomach Stomach	High High	Anaplastic carcinoma	Pancreas	Simultaneously
9	F	54	Stomach Stomach	Very low Very low	Myelogenous leukemia	Bone marrow	Simultaneously
10	M	66	Stomach	Very low	Tubulovillous adenoma	Colon	GIST 2 months later
11	F	63	Small intestine	Very low	Mucinous cystadenoma	Pancreas	Simultaneously
12	M	62	Small intestine	Very low	Tubular adenoma	Colon	GIST 5 months earlier
13	M	63	Small intestine	Very low	Ductal adenocarcinoma	Pancreas	Simultaneously
14	M	63	Small intestine	Low	Adenocarcinoma	Rectum	Simultaneously
15	M	44	Small intestine	Very low	Adenocarcinoma	Colon	Simultaneously
16	F	66	Small intestine	Very low	Adenocarcinoma	Rectum	Simultaneously
17	F	74	Small intestine	Very low	Adenocarcinoma	Colon	Simultaneously
18	M	61	Small intestine	Low	Ductal adenocarcinoma	Pancreas	Simultaneously
19	F	71	Small intestine	Low	Ductal adenocarcinoma	Pancreas	Simultaneously
20	F	70	Esophagus	Very low	Adenocarcinoma Tubular adenoma	Stomach	Simultaneously
21	M	50	Esophagus	Very low	Keratinizing squamous cell carcinoma	Stomach	Simultaneously
22	M	76	Esophagus	Very low	Adenocarcinoma	Stomach	Simultaneously

GIST, gastrointestinal stromal tumor

GIST, in two it was found before the diagnosis of the GIST, and in two following the diagnosis of the GIST. In two patients, two separate GISTs were found in the same organ. For simplicity, because of the similar nature of the two foci in these patients, in further analyses each of these two patients (and not each tumor) was considered a single case. In two patients, a GIST coexisted with an adenocarcinoma in the stomach, with the different histological structures separated by the normal gastric wall. The characteristics of the patients with GISTs are shown in Table 3.

Patients 1 and 2 had submitted to partial gastrectomy for chronic peptic ulcer. The diagnosis of a GIST and gastric adenocarcinoma were first made on histopathological examination of the surgical specimen. In patient 3, a GIST with a high risk of aggressive behavior in the stomach was diagnosed 6 months after surgery for colon cancer. In patient 4, a GIST in the stomach was discovered incidentally during surgery for colonic adenocarcinoma. Patient 5 was submitted to surgery for a tumor in the colon. During laparotomy, two focal lesions were found in the liver (which proved to be metastatic colon cancer on histopathological examination), and a 7-cm GIST was found in the stomach. In patient 6, a GIST was found in the stomach during autopsy. The patient, who had acromegaly, had died from colonic adenocarcinoma with liver metastases. The autopsy examination also revealed a 2-cm hypophyseal adenoma. Immunohistochemical examination showed the presence of growth hormone in the tumor cells. In patient 7, a GIST was found during surgery for uterine leiomyomas. Five months later, a colonic tubular adenoma and an adenocarcinoma derived from an adenomatous polyp were found during colonoscopy. Both tumors were completely resected endoscopically. In patient 8, two tumors in the gastric wall, measuring 7 and 8 cm in diameter and a 10-cm tumor of the pancreas infiltrating the small intestinal mesentery were found during laparotomy.

Histopathological examination revealed two GISTs with high risk of aggressive behavior in the stomach and an anaplastic tumor of the pancreas. In patient 9, two GISTs with very low risk of aggressive behavior were found during autopsy. The patient died from myelogenous leukemia. In patient 10, a GIST was an incidental finding during cholecystectomy. Two months earlier, the same patient underwent endoscopic resection of a colonic tubulovillous adenoma. In patient 11, a GIST was found during partial pancreatectomy for a mucinous cystadenoma. Patient 12 presented with a tubular adenoma in the colon on colonoscopy, performed 5 months after surgical resection of a GIST in the duodenum. Patients 13, 18, and 19 had submitted to pancreatoduodenectomy for pancreatic ductal adenocarcinoma, and a GIST was found incidentally during surgery. In patients 14–17, a benign GIST in the jejunum were found during surgery for colorectal cancer. In patients 20, 21, and 22, a GIST localized in the distal esophagus were incidentally found during surgery for malignant gastric tumor. To our knowledge, no cases of GISTs coexisting with hypophyseal adenoma (case 6), anaplastic carcinoma of pancreas (case 8), or mucinous cystadenoma of pancreas (case 11) have been reported previously.

The study group of 22 patients with a GIST and other neoplasms included 12 men (54.5%), and that of 60 patients with a GIST alone included 26 men (43.3%) ($P = 0.4$). In the first group, the median (interquartile range) and mean (standard deviation) age were 63.0 (58–68) and 62.3 (9.7) years, and in the second, they were 61.5 (45–65) and 57.0 (16.3) years, respectively ($P = 0.2$). In patients with a GIST and other neoplasms, the most common localization of the GIST was the stomach (ten cases, 45.5%), small intestine (nine, 40.9%), and esophagus (three, 13.6%). In patients without accompanying neoplasms, the most common localization of the GIST was the stomach (35 cases, 58.3%), followed by the small intestine (13, 21.7%), large intestine (11, 18.3%), and esophagus (1, 1.7%). GIST tended to be more common in the small intestine, compared with other localizations, in patients with a GIST accompanied by other neoplasms than in patients with a GIST alone [localization in the small intestine vs. other localizations: odds ratio (OR), 2.50; 95% CI, 0.8–7.2; $P < 0.09$). No intergroup differences in the incidence of a GIST in the stomach (vs. other localizations, $P = 0.3$), esophagus (vs. other localizations, $P = 0.1$), or colon (vs. other localizations, $P = 0.2$) were found. In the first group, 16 of 22 (72.7%) cases were spindle-cell GIST, and 34 of 60 (56.7%) in the second group. Two of 22 (9.1%) cases in the first group were epitheloid GIST, and five of 60 (8.3%) in the second group. The remaining tumors (4/22, 18.2%, and 21/60, 35%, respectively) showed a mixed pattern. No differences between the two study groups in the incidence of spindle-cell tumors (vs. other types, $P = 0.2$), epithelioid tumors (vs. other types, $P = 0.1$), or mixed types (vs. other types, $P = 0.1$) were found. GISTs with a very low risk of aggressive behavior were significantly more common in the first group (14/22, 63.6%) than in the second (23/60, 38.3%) (proportion of very low-risk GIST vs. other-risk GIST: OR, 2.82; 95% CI, 1.01–8.0; $P < 0.05$). GISTs with a low, intermediate, or high risk of aggressive behavior accounted for four (18.2%), one (4.6%), and three (13.6%) cases in the first group and 20 (33.3%), 12 (20%), and 5 (8.3%) cases in the second group, respectively. No differences in frequency between groups of GIST with low, intermediate, or high risk of aggressive behavior were found (proportion of low-risk GIST vs. other-risk GIST, $P = 0.2$; proportion of intermediate-risk GIST vs. other-risk GIST, $P = 0.1$; proportion of high-risk GIST vs. other-risk GIST, $P = 0.3$). Small intestinal GISTs with very low risk of aggressive behavior (vs. remaining GIST irrespective of localization or risk of aggressive behavior) were significantly more common in the first group than in the second (OR, 7.13; 95% CI, 1.6–37.2; $P < 0.05$). A positive immunohistochemical reaction to CD117 was present in 100% of GIST in both study groups. A positive reaction to CD34, and focal SMA and S100 positivity was observed in 12 (54.6%), 7 (31.8%), and 1 (4.6%) cases in the first group, and 34 (56.7%), 12 (20%), and 8 (13.3%) cases in the second group, respectively. There were no differences between groups in terms of CD34, SMA, or S100 reactivity ($P = 0.9$, $P = 0.3$, and $P = 0.5$, respectively).

Discussion

The coexistence of GISTs with other neoplasms has been widely addressed in literature. Special attention should be paid to the fact that the percentage of patients with a GIST in whom other neoplasms were diagnosed ranges between 2.95%[33] and 33.33%.[34] Agaimy et al.[56] described 295 (9.2%) cases of secondary tumors among a population of 2809 patients with GIST. Most common secondary neoplasms were colorectal cancer, prostate cancer, and neoplasms derived from lymphoid tissue. In their literature review, Agaimy et al.[56] found 444 (9.3%) cases of secondary malignancies among 4777 patients with GIST. The most common secondary neoplasms were colorectal cancer, gastric cancer, and prostate cancer.[56] They reported 17 (2.1%) cases of pancreatic cancer diagnosed among 813 patients with GIST and other neoplasms. In the present study, five (22.7%) cases of pancreatic tumors were found among the 22 patients with GIST and other neoplasms, because patients with pancreatic diseases were overrepresented in the present study. Additional difficulties arise because

in some studies the proportion of tumors coexisting with GIST include exclusively malignant tumors, while in other studies all neoplasms, benign or malignant, are considered.

In the present study, GISTs with very low risk of aggressive behavior were significantly more frequent in patients with other neoplasms. These were mostly asymptomatic GISTs found incidentally during surgery. Altogether, among patients with a GIST accompanied by other neoplasms, 16 of 22 (72.7%) cases were found incidentally during surgery and two of 22 (9.1%) were found incidentally on autopsy. Importantly, the proportion of symptomatic and incidentally found GISTs among patients with other tumors in a population-based study[4] was reversed. In this study, among 60 patients with a GIST without other neoplasms, only 13 (21.7%) were incidentally found during surgery. Incidental GISTs were more frequent in patients with a GIST and other neoplasms than among patients with a GIST only (OR, 9.64; 95% CI, 3.1–30.8; $P < 0.001$). None of the GISTs with no other accompanying neoplasms were found during autopsy.

Disease syndromes in which coexistence of GIST and other neoplasms may share a common ethiopathogenesis have been identified.[16] GISTs may develop in patients with type I neurofibromatosis.[7,14,33,43,49,51,52,57,58] Also, a syndrome called Carney's triad is characterized by the coexistence of at least two tumors, an extra-adrenal paraganglioma and a pulmonary chondroma, with a GIST, usually localized in the stomach.[2,7,9,16,33,59,60] So far, a few dozen cases of this syndrome have been reported.[2,59] It is supposed that the development of a GIST in patients with Carney's triad is associated with a different mutation than that associated with a sporadic GIST.[60] The role *C-KIT* or *PDGFRA* mutations in the pathogenesis of sporadic GISTs is well documented, but their role in the pathogenesis of GISTs developing in patients with type I neurofibromatosis or Carney's triad is more controversial.[9,57,58,60] In patients with Carney's triad, no significant response to imatinib is observed.[60] GISTs accompanying jejunal paraganglioma[9] and a GIST in a patient with multiple endocrine neoplasia type 1 (MEN 1)[61] have been reported, as well as cases of familial GISTs.[2,7,10,62–66] Familial GISTs are associated with the *C-KIT* gene or a *PDGFRA* germline mutation.[62–66]

Careful differential diagnosis of patients with a GIST and neurofibromatosis from those with a sporadic or metastatic GIST or with familial GIST is needed.[56] Cases of multiple GISTs constitute a separate issue.[67] Multiple GISTs may develop in patients with a germline mutation; however, multiple GISTs have been reported in a child with no family history and without any of the common *C-KIT* and *PDGFRA* mutations in the tumor tissue.[67]

It has not been established whether the coexistence of a GIST with other, unrelated syndromes or tumors is incidental or results from related pathophysiological processes.[21,22,24,29–31,36,48] Coexisting tumors may be favored by a high incidence of tumors among the given population.[22,36,48] This relationship is difficult to assess and define since these mostly benign GISTs are not recorded in cancer statistics.[4,15,48] As a result, epidemiological data may be incorrect. Moreover, the terminology and diagnostic criteria of GISTs have been established only recently.[4] A few experimental data show that a single carcinogen may induce neoplastic transformation in cell lines of various histotypes.[68] It has been proposed that simultaneous neoplastic proliferation of epithelial and stromal cells might be stimulated by the same carcinogenic factor.[21,22] In addition, gene mutations predisposing to the development of various types of neoplasms may play role.[22,32,36] Au et al.[32] proposed that the coexistence of a GIST with renal papillary carcinoma may result from mutation of protooncogenes coding thyrosine kinases, *C-KIT* and *C-MET*, respectively. This phenomenon may be analogous to the *C-RET* protooncogene mutation observed in multiple endocrine neoplasia (MEN 2A). Frequent *C-KIT* and *C-MET* coexpression in solid tumors may indirectly indicate common regulatory mechanisms.[32] The presence of a mutation or deregulated *C-KIT* expression apart from a GIST is also observed in chronic myeloid leukemia, germ cell tumors, small cell carcinoma of the lung, neuroblastoma, melanoma, ovarian carcinoma, breast carcinoma, and colorectal carcinoma.[35,56,69] Melis et al.[36] failed to find unequivocal evidence of common mechanisms in the pathogenesis of GISTs and colorectal adenocarcinoma. In their case report on the coexistence of primary gastric carcinoma with mucosa-associated lymphoid tissue lymphoma and stromal tumor, Kaffes et al.[20] indicated that *Helicobacter pylori* infection was a favoring factor. However, other researchers claim this hypothesis is inconsistent with the high incidence of *H. pylori* infection compared with the low incidence of GISTs.[29,46] In addition, impaired immunity, constitutional and genetic factors, chemotherapy, exposure to ionizing radiation, surgery, and tobacco smoking, all of which predispose to multifocal neoplasia,[42,44] may play a role. Moreover, the population of patients with a GIST coexisting with other tumors may be older than the that of patients without accompanying neoplasms;[28] however, this is not reflected by the results of the present study. Patients with Carney's triad are an exception.[2,16,59] Kalmar et al.[27] found that the frequency of malignant neoplasms among patients with a GIST (21.7%) is significantly higher than that in the general population (4%; $P < 0.001$). Some authors suggest that there is no relationship between the development of GISTs and other tumors, and their coexistence is only coincidental.[31,46]

The problem of the coexistence of GISTs with other neoplasms is important from the viewpoints of oncology, surgery, and histopathology:[28]

1. GIST may be a focal lesion (found predominantly during a visualization examination) in a patient with another neoplasm, diagnosed during staging. Failure to obtain a sample for microscopic examination may result in an incorrect clinical decision.
2. GISTs may by found incidentally during surgery performed for another reason. This may affect intraoperational therapeutic decisions and result in changes to the planned surgical approach.
3. Another difficulty in management of patients with other tumors is that a GIST found during follow-up after treatment for another tumor requires that local recurrence be differentiated from metastasis.
4. Cases of GISTs found during procedures for determining the localization of the primary tumor in patients with liver metastases constitute a separate category.[28]
5. Diagnosis of a focal lesion in the liver in patients with a previously diagnosed malignant GIST is another difficult problem.[70] The focal lesion in the liver of a patient with a GIST may also be a primary tumor.[37] There are some discrepancies regarding the value of preoperative core-needle biopsies in patients with a GIST.[3]

The search for causal relationships underlying the coexistence of GISTs with other neoplasms is of special importance for understanding the nature of pathophysiological processes and the natural history of disease in patients with a GIST. Recently, an alternative approach to causal relationships has been proposed by Lipton and Odegaard,[71] who reported that for the purpose of epidemiology, one could give up finding the causal relationship and instead focus on establishing associations enabling effective prediction and/or intervention. In the five clinical situations listed above, such an approach seems to yield encouraging results.

In conclusion, we found numerous cases of GISTs coexisting with other neoplasms. Coexistence with other neoplasms was found in almost 27% of patients. The most common association was a GIST with colorectal or gastric adenocarcinoma or pancreatic ductal adenocarcinoma. We observed a tendency toward a more common incidence of GISTs in the small intestine, in comparison with other localizations, in patients with a GIST accompanied by other neoplasms than in patients with a GIST alone. Tumors with very low risk of malignant behavior were significantly more common in the first group than in the second. GISTs found incidentally during surgery were also more common in the first group than in the second. No significant differences in immunohistochemical profile between GISTs in the two study groups were observed. The percentage of patients with a GIST in whom another tumor was diagnosed was relatively high in this study in comparison with cases reported in the literature. However, this finding should be interpreted with care owing to substantial differences in methods of data selection for analysis and in the duration of observation. Undoubtedly, the type of study center affects the results by determining the nature of the material used for detailed examinations.

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