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Additional Primary Malignancies in Patients with Gastrointestinal Stromal Tumor (GIST): A Clinicopathologic Study of 260 Patients with Molecular Analysis and Review of the Literature

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Abstract

Background—The incidence of other primary neoplasms in gastrointestinal stromal tumor (GIST) patients is relatively high. Our aim was to better characterize the clinicopathologic and molecular relationships in a cohort of GIST patients.

Methods—All GIST patients with tumor samples sent for molecular testing were identified via electronic medical records. Clinicopathologic characteristics of GIST and additional primary malignancies were analyzed.

Results—Of 260 patients, 50 (19 %) had at least one additional primary malignancy. In 33 patients, separate primary neoplasms predated their GIST diagnosis and most commonly included: prostate ($n = 9$), breast ($n = 8$), and hematologic ($n = 5$). Renal ($n = 4$) and hematologic ($n = 3$) malignancies were the most frequent cancers identified after GIST diagnosis. The majority (8 of 12, 66 %) of malignancies diagnosed after GIST were found incidentally. Patients who developed other malignancies after GIST more often had *KIT* exon 11 mutations (100 vs. 66 %, $P = 0.01$). In comparison to patients with only GIST, patients with a second primary neoplasm of any chronology had GISTs with increased mitotic rate (5 per 50 high-power fields) ($P = 0.0006$). Literature review revealed colorectal cancer, gastric, prostate, renal, leukemia, and desmoid-type fibromatosis as the most common secondary neoplasms.

Conclusions—Nineteen percent of GIST patients develop other malignancies. This is the first report to describe a relationship between additional primary malignancy and both mutation and

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mitotic rate of GIST. Although the basis of these relationships remains to be investigated, caution in the clinical management of GIST patients with additional lesions is warranted.

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal tract, with an annual incidence of 11–19 per million.^{1,2} Activating mutations of *KIT* and *PDGFRA* occur in approximately 90 % of all GISTs, with *KIT* exon 11 deletions occurring in 34 % of cases, *KIT* exon 11 substitutions occurring in 15.5 % of cases, *PDGFRA* mutations in 12.9 % of cases, *KIT* exon 11 duplications in 7 % of cases, and *KIT* exon 9 mutations in 7 % of cases.^{3,4}

The majority of GISTs develop sporadically; however, germline mutations in *NF1*, the succinate dehydrogenase (SDH) complex, or *KIT* have linked GISTs to other tumors, including nerve sheath tumors, paragangliomas, pulmonary chondromas, and multiple GISTs.⁵ More recently, it has become apparent that patients with sporadic GIST have an increased incidence of other cancers, and those with multiple cancers have relatively increased mortality.^{6,7} The nature of these relationships remains unknown.

We retrospectively analyzed all GIST patients whose tumors (primary and/or metastases) underwent molecular analysis at Memorial Sloan Kettering Cancer Center for the incidence of additional malignancies. Clinical, histopathologic, and molecular correlations and review of the literature are discussed.

METHODS

Patients

After approval by the institutional review board at Memorial Sloan Kettering Cancer Center, we searched records of the laboratory of diagnostic molecular pathology to identify all patients with GIST whose tumor sample underwent molecular analysis from 2009 to 2013. Data including demographics, social and family history, date of diagnosis, presentation, stage, histologic type, mitotic rate ≤ 5 or > 5 per 50 high-power fields (HPF), and treatment received were retrieved from electronic medical records. The mitotic rate recorded was that of pretreatment resection material if available, and of pretreatment biopsy material if neoadjuvant therapy was received.

In addition to malignancies with the ability to metastasize, we recorded cases of locally aggressive neoplasms including recurrent cranial tumors, abdominal fibromatosis, and diffuse pigmented villonodular synovitis. Squamous and basal cell carcinomas of the skin and benign neoplasia were excluded.

Molecular Analysis of GISTs

Formalin-fixed, paraffin-embedded tumor samples were screened for insertions and deletions with a sizing assay. Briefly, *KIT* exons 9 and 11 indels were detected by length analysis of fluorescently labeled polymerase chain reaction (PCR) products on a capillary electrophoresis instrument (ABI 3730).

Cases that were negative were reflexed to Sanger sequencing of *KIT* exons 9, 11, 13, and 17 and *PDGFRA* exons 12 and 18. The entire coding regions of these exons were amplified by PCR in duplicate using HotStart Taq DNA polymerase and appropriate primers. The PCR products were purified using Spin Columns (Qiagen) and sequenced using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) according to the manufacturer's protocol on an ABI 3730 running ABI Prism DNA Sequence Analysis Software. All PCR products were sequenced with forward and reverse primers.

Statistical Analysis

Comparisons among the following patient groups were performed by the Chi square test: (1) GIST only, (2) GIST with previously diagnosed malignancy, (3) GIST with synchronous malignancy, and (4) GIST with subsequent malignancy. Survival analyses of whole cohort and subgroups based on risk or progression (very low/low, medium, and high) using criteria by Miettinen and Lasota were assessed with Kaplan–Meier curves.⁸ A *P* value of less than 0.05 was considered significant.

RESULTS

Overall Patient and GIST Characteristics

Of 260 patients with GIST and molecular testing, 50 patients (19.2 %) had one or more additional non-GIST malignancy or malignancies. Patient characteristics are summarized in Table 1.

A total of 206 patients (80 %) received imatinib, either before (neoadjuvant) or after (adjuvant) surgical resection. Of those, 195 patients were positive for *KIT* or *PDGFRA* mutation. The remaining patients elected to pursue observational management. Eleven patients without *KIT*/*PDGFRA* mutation received imatinib. Seventeen (8 %) of 210 GISTs were incidental findings in the GIST only group, 10 (20 %) of 50 GISTs in patients with other malignancies were incidental findings, and an overall 27 (10 %) of 260 of GISTs in this study were incidental.

Median follow-up time for all GIST patients was 33 months (range 0–324 months), and survival was approximately 50 % at 50 months (Fig. 1a). Subgroup analysis based on risk of progression (very low and low vs. intermediate vs. high) revealed no significant difference in median follow-up time (28, 27, and 38 months, respectively) or overall survival (*P* = 0.58) (Fig. 1b). There was also no association between risk of progression of GIST and history of cancer in any immediate family member (*P* = 0.87).

Patients with Additional Primary Malignancies

Patient characteristics are summarized in Table 1. Second primary neoplasms were diagnosed before GIST in 33 patients (12.7 %), synchronous to GIST in 5 patients (1.9 %), and after GIST in 12 patients (4.6 %). Seven patients (2.7 %) had more than one malignancy diagnosed before GIST. Anatomic distribution for GIST in this group was as follows: 28 (56 %) gastric, 19 small intestinal (38 %), 1 esophageal (2 %), 1 colorectal (2 %), and 1 (2 %) with local abdominal spread with primary site unknown.

Of 33 patients in whom previous cancers occurred before GIST, 19 (57.6 %) were men. The median and mean age at GIST diagnosis for this group was older than all other groups, at 66 and 63.5 years, respectively. Other primary neoplasms were diagnosed from 2 to 39 years (mean 18.6, median 8) before GIST. Prostate ($n = 9$) and breast ($n = 8$) were the most common disease sites. Distribution of other primary neoplasms is summarized in Table 2 and Supplementary Table 1. Treatment for other primary neoplasms previous to GIST included the following: chemoradiation ($n = 7$, 20 %), radiotherapy ($n = 5$, 15 %), chemotherapy ($n = 3$, 9 %), radioactive iodine ($n = 1$, 3 %), and 10 years of imatinib for chronic myelogenous leukemia ($n = 1$, 3 %). The GISTs in this group included 22 (66.7 %) gastric, 10 (30.3 %) small intestinal, and 1 (3 %) esophageal GIST. The distribution of GIST mutations in this group was not statistically different than the group that developed GISTs alone and included 13 (39.4 %) *KIT* exon 11 deletions, 8 (24.2 %) *KIT* exon 11 missense mutations, 1 (3 %) *KIT* exon 11 insertion, 2 (6.1 %) *KIT* exon 13 mutations, 2 (6.1 %) *KIT* exon 9 mutations, 5 (15.2 %) *PDGFRA* exon 18 mutations, and 2 (6.1 %) wild-type GISTs.

The five patients with synchronous primary neoplasms included four patients (two men, age range 45–77 years, mean 62.5 years) in whom a more indolent non-GIST primary neoplasm was diagnosed at the time of GIST workup or resection, as follows: papillary thyroid carcinoma metastatic to locoregional nodes, well-differentiated pancreatic neuroendocrine tumor, appendiceal carcinoid, and ruptured appendiceal mucinous neoplasm of uncertain malignant potential. The GISTs of these patients included three small intestinal and one gastric. All four patients' GISTs harbored *KIT* exon 11 deletions. The fifth patient, a 32-year-old woman being assessed for a diagnosis of Hodgkin lymphoma, had a small (2 cm) gastric GIST with high mitotic rate that was negative for mutations in *KIT* and *PDGFRA*.

Twelve patients developed a secondary malignancy after GIST. Nine (75 %) were men. Age ranged from 46 to 77 years, with a mean of 61.2 years and median of 65 years. Secondary malignancies developed from 5 months to 6 years after GIST, with mean of 2.5 and median of 2 years. Eight (66 %) of 12 of malignancies were incidentally diagnosed during GIST follow-up. This group included renal cell carcinoma ($n = 4$), prostate carcinoma ($n = 2$), papillary thyroid carcinoma ($n = 1$), hematologic malignancies including mycosis fungoides ($n = 1$), chronic lymphocytic leukemia ($n = 1$), myelodysplastic syndrome with 5q deletion ($n = 1$), and desmoid-type fibromatosis ($n = 1$). Ten (83.3 %) of these patients received imatinib before their second malignancy. Mean, median, and range of imatinib duration before diagnosis of secondary malignancy was 25.7, 19, and 5–62 months, respectively. Anatomic locations of GIST included 6 (50 %) small intestine, 4 (33 %) gastric, 1 (8 %) colorectal, and 1 (8 %) with local abdominal spread with primary site unknown. All 12 patients in this group had *KIT* exon 11 mutation including 5 (41.6 %) missense, 6 deletion (50 %), and 1 (8 %) insertion mutation. There was no statistically significant association between the development of a secondary malignancy and the use of imatinib ($P = 0.74$). However, *KIT* exon 11 mutations ($P = 0.01$), including *KIT* exon 11 missense mutations ($P = 0.04$), were increased. When we compared mitotic rates, increased mitotic rate in GIST ($\geq 5/50$ HPF) was associated with secondary malignancy ($P = 0.0006$). Increased mitotic rate did not correlate with mutation type.

DISCUSSION

In summary, we find that about 20 % of GIST patients develop a second primary malignancy. In comparison, Surveillance, Epidemiology, and End Results data using an age-matched population shows that the overall risk of developing any type of cancer in both men and women is approximately 10 %.⁹

Recent interest in secondary primary neoplasms in patients with GISTs outside of the spectrum of SDH deficiency-related syndromes and neurofibromatosis type 1 has sparked several retrospective studies. Other studies have documented other primary malignancies in 4.5–33 % of GIST patients.^{6,7,10} The largest 2 studies documented second primary neoplasms in 9.2 and 20 % of GIST patients.^{7,10} A review of the literature yielded 558 separate primary neoplasms in patients with GIST before the current report (Tables 2, Supplementary Table 1).^{7,10–15} Together with our data, 608 separate primary neoplasms have been reported, including 169 other primary neoplasms preceding GIST, 56 primary neoplasms synchronous to GIST, and 89 primary neoplasms after GIST. Although the reported spectrum of separate primary neoplasms is wide, several trends exist.

First, gastric carcinoma was the most common synchronous other primary neoplasm described in the literature. Theories to explain this phenomenon include finding GIST incidentally during carcinoma workup, or shared factors of the gastric microenvironment playing a role in the formation of both carcinoma and GIST. In support of the former theory, our cohort lacked gastric carcinoma, while their GISTs were more often large and mitotically active high-risk tumors (nonincidental), necessitating molecular testing.

Second, common cancers, including breast and prostate carcinoma, are also common in GIST patients. Review of the literature yielded 70 cases of prostate carcinoma and 43 cases of breast carcinoma in GIST patients. In our series, 8 patients had breast carcinoma and 9 patients had prostate carcinoma before developing a GIST. Although chemotherapeutic drugs can be carcinogenic, the best-known therapy-induced secondary malignancies are hematologic.^{16,17} Eleven of 33 patients with second primary neoplasms preceding GIST in our series received chemotherapy.

Third, renal cell carcinoma, including both papillary and clear cell types, both of which were seen in our series, seems to occur at a relatively high incidence in GIST patients, without an apparent chronologic relationship. Whether certain patients have genetic susceptibility toward both GIST and renal cell carcinoma or whether increased imaging to follow GIST progression plays a role remains to be determined. Imatinib is indeed reported to cause genitourinary carcinogenesis in rodents.^{18,19} However, lack of statistical evidence in our series, when comparing the incidence of subsequent malignancy in patients who received imatinib versus those who did not receive imatinib, and the lack of reported renal cell carcinoma in patients who receive imatinib for chronic myelogenous leukemia do not support the role of imatinib in the development of renal cell carcinomas in these patients. Interestingly, renal cell carcinomas have been shown to express KIT and its ligand, stem cell factor, by immunohistochemical analysis, yet activating mutations have not been reported.²⁰

Fourth, patients with GIST occasionally develop desmoid-type fibromatosis with nuclear beta catenin expression and *CTNNB1* mutations.¹² Although desmoid-type fibromatosis is rare, it occurs at higher frequency at postsurgical and trauma sites. Dumont et al. reported a series of 28 cases of desmoid-type fibromatosis occurring in patients with GIST.¹² Some tumors harbored *CTNNB1* mutations, and the majority of desmoid-type fibromatosis (75 %) developed after GIST. Because 10–30 % of desmoid-type fibromatosis develop in postsurgical patients, these tumors remain in the differential diagnosis in cases of possible clinical recurrence of GIST.²¹

Several articles have pointed out the occurrence of other *KIT*-mutated malignancies in patients with GIST. There were two seminomas and three melanomas in the current series, all before GIST. GISTs in patients with seminoma harbored *KIT* exon 11 missense mutation and *PDGFRA* exon 18 deletion. All three GISTs in patients with a history of melanoma were positive for *KIT* exon 11 deletions. In contrast, seminomas usually harbor exon 17 missense mutations, while melanomas usually harbor exon 11 missense mutations.^{22,23} Therefore, our data do not support a link between a specific *KIT* mutation and these malignancies.

In the analysis of the *KIT*/*PDGFRA* mutations in GIST and the presence of other primary neoplasms, we did not detect any relationship between *KIT* or *PDGFRA* mutations in GISTs and other malignancies before or synchronous to GIST. However, we did find a statistically significant correlation between *KIT* exon 11 mutations ($P = 0.01$) and subsequent malignancies compared to all patients who did not develop a subsequent malignancy. Although *KIT* exon 11 missense mutations trended with subsequent malignancy in our cohort ($P = 0.04$), our cohort was subject to selection bias due to analysis of cases sent for molecular testing and was also limited in number. Because the vast majority of reported cases and studies on patients with GISTs harboring other primary neoplasms do not include the molecular status of GISTs, larger numbers of cases are needed to further explore this relationship. We also found that increased mitotic rate in GIST ($\geq 5/50$ HPF) was associated with a secondary malignancy of any chronology ($P = 0.0006$). This is a novel observation, and the basis for this finding could be quite complex, possibly involving unidentified genetic features. Similar correlation was not seen with tumor size.

Most importantly, these patients require caution in clinical management. Because one-fifth of patients with GIST harbor or will develop other malignancies, a thorough workup in patients who present with gastrointestinal symptoms, such as bleeding or pain, should be performed because more than one type of malignancy may be present. New clinical or radiologic masses in patients with history of GIST should be sampled via biopsy to exclude a non-GIST malignancy. The pathology of these patients may create pitfalls because collision tumors involving subtle signet ring cell carcinomas have been reported.⁸ Lymphocytes within GISTs may also create a diagnostic pitfall because they may either be nonneoplastic tumor-infiltrating lymphocytes or neoplastic small lymphocytes. For example, in our series, we had one case of chronic lymphocytic leukemia involving a GIST. The difference between these low-grade B cell lymphomas involving a GIST and tumor-infiltrating lymphocytes, which are often prominent in GISTs, can be resolved with immunohistochemistry, yet can be subtle on hematoxylin and eosin stained sections in biopsy material.^{24–26} Histologic clues of a neoplastic lymphocytic infiltrate include both

aggregate and nodule formation, while tumor-infiltrating lymphocytes may aggregate around fibrovascular structures or appear singly but do not usually form nodules.

In conclusion, we have presented a series of patients with second malignancies associated with GIST tumors. Further studies investigating whether certain GIST patients are genetically more susceptible to the development of second cancers may better define patient subsets and help direct appropriate surveillance and clinical management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

Overall survival of GIST patients. **a** Survival rate of 50 % occurs at approximately 50 months. **b** No statistically significant survival difference was observed between GIST patients with different estimated progression risks

TABLE 1

Characteristics of 260 patients with GIST

Characteristic	Chronology of non-GIST additional primary neoplasms					<i>P</i> ^a
	GIST only	Previous other cancer	Synchronous other cancer	Subsequent other cancer	Total	
Gender						
Male	112	19	2	9	142	0.39
Female	98	14	3	3	118	
Age at GIST diagnosis						
Mean	56.9	63.5	56.4	61.2		
Median	57	66	64	64.5		
Range	24–88	30–85	32–77	46–73	24–88	
Anatomic site of GIST						
Stomach	96	22	2	4	124	0.19
Small Intestine	89	10	3	6	108	0.57
Unspecified	12	0	0	1	13	
Colorectum	8	0	0	1	9	0.65
Esophagus	2	1	0	0	3	0.44
Omentum	3	0	0	0	3	0.44
Mitotic rate of GIST						
<5/50 HPF	120	12	2	3	137	0.0006
5/50 HPF	68	18	3	9	98	
Unknown	22	3	0	0	25	
Size of GIST, cm						
Mean	9.9	7.7	7.0	9.1		
Median	8	6.1	6	7.4		
Range	0.3–50	1.4–34	2–11.9	3–13.5	0.3–50	
Molecular status of GIST						
<i>KIT</i> exon 9	23	2	0	0	25	0.13
<i>KIT</i> exon 11 deletion	94	13	4	6 ^b	117	0.87
<i>KIT</i> exon 11 missense	35	8	0	5 ^b	48	0.13

Characteristic	Chronology of non-GIST additional primary neoplasms				<i>P</i> ^a
	GIST only	Previous other cancer	Synchronous other cancer	Subsequent other cancer	Total
<i>KIT</i> exon 11 insertion	9	1	0	1 ^b	11
<i>KIT</i> exon 13 missense	6	2	0	0	8
<i>PDGFRA</i> exon 12	5	0	0	0	5
<i>PDGFRA</i> exon 18	21	5	0	0	26
Wild type	17	2	1	0	20
Imatinib treatment					
Yes	171	22	3	10	206
No	39	11	2	2	54
Time between GIST and separate primary lesion, y					
Mean	–	18.6	–	2.5	–
Median	–	8	–	2	–
Range	–	2–39	–	0.4–6	–
Total cases	210	33	5	12	260

GIST gastrointestinal stromal tumor, HPF high-power field

^a GIST only versus GIST and second primary neoplasm

^b Patients who developed secondary malignancy after GIST had a higher rate of *KIT* exon 11 mutations ($P = 0.01$). This statistical difference was not observed with exon 11 mutation for additional primary lesions before or synchronous to GIST

Frequency of non-GIST additional primary neoplasm in GIST patients in current and previous studies^{6,7,10-14}**TABLE 2**

Site of non-GIST neoplasm	Before GIST		Synchronous to GIST		After GIST		Unknown chronology Previous studies	Total
	Current study	Previous studies	Current study	Previous studies	Current study	Previous studies		
Gastrointestinal	1	32	1	44	0	9	98	185
Genitourinary and adrenal	16	41	0	1	6	14	80	158
Breast	8	12	0	0	0	4	25	49
Hematologic	4	6	1	0	3	9	25	48
Soft tissue	2	5	0	6	1	27	7	48
Thoracic	1	5	0	0	0	6	21	33
Hepatobiliary	0	8	0	0	0	0	12	20
Neuroendocrine	2	0	2	0	0	0	8	12
Melanoma	3	7	0	0	0	2	7	19
Unknown primary lesion	1	7	0	0	0	3	6	17
Head and neck	4	3	1	0	2	3	3	16
Cranial total	1	0	0	0	0	0	2	3
Total	43	126	5	51	12	77	294	608

GIST gastrointestinal stromal tumor