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Second Primary Malignancies in Patients with Gastrointestinal Stromal Tumours: Ten-Year Experience from the Ottawa Hospital

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Abstract

Background: The secondary malignancies in patients with GIST are relatively high. We present our 10-year experience of SPM in patients with GIST from a regional Cancer Centre in Canada.

Methods: A retrospective cohort study was performed on all GIST patients treated at TOH between January 2011 and December 2021. Clinicopathological data were analyzed. Survival analysis was estimated using the Kaplan-Meier method and compared by log-rank test.

Results: In Total, 248 patients with GIST were identified. Of these, 61 patients (25%) had 76 SPMs; synchronous (9, 15%) and metachronous (52, 85%). Nine patients had two additional primary cancers, and four patients had three additional primary cancers. The most common SPMs were skin cancer (14, 18%), melanoma (5), and non-melanoma (9), followed by prostate cancer (13,17%) and breast cancer (12,16%). Colorectal cancer and hematological malignancies were found in (5, 7%) (9,12%) patients, respectively, while RCC was found in (4, 5%). Based on Miettinen risk classes for non-metastatic GIST, 74% had zero to low-risk disease, while 26% had moderate or high-risk disease. The median follow-up time was 53 months (range 1 – 132). Five years overall survival of SPM group vs. non-SPM, 79.8% vs. 94.1%, (p=0.03).

Conclusions: We observed that one out of four GIST patients have SPM. Skin, Prostate, and breast cancers were the most common SPM associated with GIST. Molecular studies are needed to explore the association/underlying mechanisms of GIST with these malignancies.

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Introduction

Despite the rarity of Gastrointestinal Stromal Tumors (GIST), The incidence of Secondary Primary Malignancies (SPM) among these patients are relatively high. The majority of GIST occur in a sporadic fashion. However, there is a well-established association between GIST and certain syndromes such as neurofibromatosis type I and Carney-Stratakis syndrome. Familial GIST is also described to have an association with other secondary malignancies [1-4]. The GIST can occur anywhere within the GI tract, but the stomach and small intestine are the two most common locations representing 60 %, and 30%, respectively. GIST located outside the GI tract; the so-called Extragastrointestinal Stromal Tumor (EGIST) is reported in less than 5% of cases. These sites include the omentum, mesentery, abdominal wall, pancreas, and spleen [5]. It is estimated that 85% of GIST cases had KIT or PDGFRA mutation. On the other hand, wild GIST, which lacks KIT or PDGFRA mutation, represents 15%. The management of GIST has significant evolution over the last two decades with the introduction of tyrosine kinase inhibitor (TKI) [6,7].

Recently there is growing evidence of the coexistence of GIST with other tumors [8]. These include GI cancers, breast cancer, clear cell carcinoma, prostate adenocarcinoma, lymphoma/leukemia, and gynecological malignancy among others. There is a discrepancy in the incidence of SPM in literature, ranging from 4% to 33% [9]. There are many questions unanswered about the association of these tumors with the GIST. It is unknown whether there are underlying genetic aberrations for the concomitant occurrence of GIST with other malignancies. Moreover, the clinical and therapeutic importance of these associations are areas for more research.

This study aims to report the incidence of secondary malignancies in patients diagnosed with GIST over the past 10 years and to explore the prognostic factors, and survival outcomes.

Materials and Methods

This is an observational retrospective cohort study. We identified GIST cases through searching hospital databases using ICD 10 codes. We examined records of all GIST cases referred to/or diagnosed in TOH between January 01, 2011 and December 31, 2021. Only patients with biopsy-proven and immunohistochemistry confirmed diagnosis of GIST were included in the study. After identifying cases with secondary malignancies. Details of the tumour site, risk assessments, clinical, pathological, management and outcomes data were recorded. Risk assessment was estimated according to Miettinen risk criteria. Data collected from the electronic medical records (Epic) on access database. Results were analysed using MS Excel and SPSS 25.0 software. Descriptive statistics used to summarize data, synthesize and report patients' demographic and clinicopathological data. Qualitative variables were analysed by $\chi 2$ test and Fisher's exact test. Survival data analysed using Kaplan–Meier methods and compared by log-rank test. OS was calculated from the date of tissue diagnosis to date of death or last follow up. Potential prognostic factors analysed using the Cox proportional hazard model for multi-variate analysis. Two-tailed P-values were reported and were considered to be statistically significant when $P < 0.05$.

Results

We screened 248 GIST cases diagnosed between 2011-2021. We identified (n=61) patients had SPM representing 24.6%. Nine patients had two additional primary cancers, and four patients had three additional primary cancers.

Patient's characteristics

All patients' characteristics summarised in **table 1**. Mean age was 69 (range 44-90). Males were 59% while females 41%. In 56% (n=34), the diagnosis of GIST was incidental finding. The initial diagnosis of GIST was made by CT scan in 63% of cases.

Table 1: Baseline patient's characteristics.

		n = 61	(%)
Age	Median	70 (Range 44 – 90)	
Gender	Male	36	(59)
	Female	25	(41)
Comorbidities	HTN	30	(49.2)
	DM	12	(19.7)
	DLP	27	(44.3)
	GERD	5	(8.2)
	IHD	7	(11.5)
	Neurofibromatosis	1	(1.6)
Clinical presentation	Incidental	34	(55.7)
	Abdominal pain	10	(16.4)
	GI bleeding	11	(18)
	Anaemia	8	(13.1)
	Bowel obstruction	2	(3.3)
	Other	10	(16.4)
Duration of symptom	<14 days	6	(9.8)
	>14 day	3	(4.9)
	>2months	9	(14.8)
	>6months	6	(9.8)
	NA	5	(8.2)
ECOG	0	27	(44.3)
	1	20	(32.8)
	2	1	(1.6)
	3	1	(1.6)
	NA	12	(19.7)
Mode of initial diagnosis	CT	39	(63.9)
	Endoscopy	9	(14.7)
	Surgical exploration	6	(9.7)
	Ultrasound	2	(3.2)
	EUS	4	(6.6)
Curative surgery		47	(77)
Observation		5	(8.2)
Palliative TKI		8	(13)

Types of secondary malignancy

Details of SPM summarised in **table 2**. The most common SPMs were skin cancer (14, 18%), melanoma (5), and non-melanoma (9), followed by prostate cancer (13, 17%) and breast cancer (12, 16%). Colorectal cancer and hematological malignancies were found in (5, 7%) (9,12%) patients respectively, while RCC was found in (4, 5%). Thyroid cancer, lung cancer, neuroendocrine tumor, bladder cancer, thymoma, and other types of cancers were collectively found in 19 cases (25%).

Table 2: Secondary malignancies.

Prostate cancer	13	(17.1)
Breast cancer	12	(15.8)
Skin-Non-Melanoma	9	(11.8)
Colorectal	5	(6.6)
Skin-Melanoma	5	(6.6)
Bladder	4	(5.3)
Lung	4	(5.3)
RCC	4	(5.3)
CLL\CML	3	(3.9)
Lymphoma	3	(3.9)
Multiple myeloma	2	(2.6)
NET	2	(2.6)
Thyroid	2	(2.6)
CNS	1	(1.3)
CUP	1	(1.3)
Gastric	1	(1.3)
Gyn	1	(1.3)
Head & neck SCC	1	(1.3)
Leukaemia	1	(1.3)
Pancreas	1	(1.3)
Thymoma	1	(1.3)

**76 SPMs in 61 patients

Timing

Majority (57%) of second primary malignancy diagnosed prior to GIST diagnosis, table 3. While 30% diagnosed following GIST diagnosis and 15 % was synchronous with GIST diagnosis.

Sites of GIST and staging

Majority was in the stomach (62%) followed by the small bowel (30%). Around 75% had TNM stage I or stage II disease, while 15% had stage IV disease at the time of diagnosis.

Pathology of GIST

69% had spindle cell histology. 13% had mixed histology while 7% had epithelioid histology.

There was no association between SPM and GIST primary site (p=0.4), TNM stage (p=0.8), histology (p=0.2), Mitosis (p=0.5), and Miettinen risk class (p=0.6).

Table 3: Sequence of Secondary malignancies.

	Total n = 61 (Percent %)	
Synchronous	9	14.8
GIST -- > 2nd cancer	17	27.9
2nd cancer -- > GIST	35	57.4

Risk assessment

Based on Miettinen risk classes for non-metastatic GIST, 74% had zero to low-risk disease, while 26% had moderate or high-risk disease.

Mutation testing

Not routinely performed. Only three patients had mutation testing.

GIST management and outcomes

Around 77% underwent curative surgical resection. 8% underwent observation only. Ten patients (16.4%) received adjuvant imatinib. Two patients (3.3%) had recurrent disease after curative treatment, including adjuvant therapy. Nine patients (15%) received systemic therapy, and at least one line of TKI.

Survival

Median follow-up time 53 months (range 1-132). A total of nine (15%) death events were documented and four patients lost follow-ups. Five years overall survival of SPM group vs. non-SPM were 79.8% vs. 94.1%, (p=0.03) **Figure 1**. Cox regression did not reveal a significant association with the covariates.

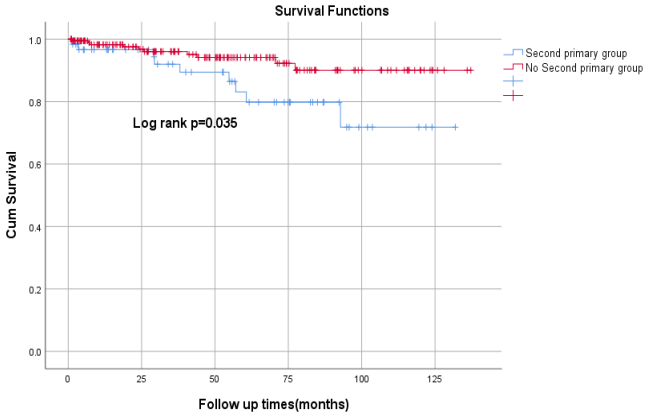

Figure 1: Overall Survival using Kaplan Meir cureve.

Discussion

Gastrointestinal Stromal Tumors (GIST) are rare non-epithelial tumors derived from mesenchymal tissues. It originates from the interstitial Cajal cells or stem cell precursors of these cells, which are located around the myenteric plexus throughout the gastrointestinal tract [10,11]. GIST account for 1-3% Of all GI tumors. Over the last two decades, there was a considerable understanding of the pathogenesis and biology of this tumor with identifying c-KIT pathway and discoveries of important mutations with clinical and therapeutic significance, including exons 11, 9,13, 17, and Platelet-Derived Growth Factor Receptor Alpha Gene (PDGFRA) [12-14]. The oncogenic mechanisms in the majority of sporadic and fa-milial GIST are linked to KIT and PDGFRA activating mutations [4]. Alternative mechanisms drive mutations leading to the development of GIST such as inactivation of NF1 or genes encoding Succinate Dehydrogenase (SDH) subunits [15]. The present study examined the incidence of SPM in patients with GIST, who were diagnosed and treated in TOH over the past 10 years. We found that the incidence of SPM is 24.6%, and the skin, Prostate, and breast cancers were the most common SPM associated with GIST. This is higher than reported from the SEER population-based study, which reported an incidence of SPM around 17% [16].

Multiple studies have shown that patients with sporadic GISTs have a higher probability of developing other primary malignancies. Diamantis A et al. conducted a review that included 10 retrospective case series with 1108 GIST patients and found an 18% had synchronous intrabdominal malignancies with most common one being gastric adenocarcinoma [8]. However, this study did not include extra GI malignancies. Agaimy A et al. found that gastric GIST have higher incidence of SPM [9]. A systematic review and meta-analysis by Petrelli et al. demonstrated a higher prevalence of gastrointestinal and genitourinary tract cancers of second primary tumors in patients with a

previous diagnosis of GIST [17].

The major types of GIST-associated cancers reported in most series were gastrointestinal carcinomas, hematological malignancies, prostate, breast, and kidney cancers. Less usual cancers included malignant melanoma [8,18]. The most notable difference in our study is that, we found higher incidence of skin cancer (melanoma and nonmelanoma), prostate and breast cancer. Of note, non-melanoma skin cancer was not reported in many studies. Although most of SPM were common tumors with increasing age, in our study the mean age is 69, more studies are needed to reveal a possible causal association or carcinogenic agents.

The time of development of SPM in relation to GIST diagnosis is varied in literature. Diamantis et al. found the frequency of the synchronous development of SPM was found to be 18% [8]. In our study, the majority (57%) of SPM were diagnosed prior to GIST diagnosis.

GISTs have been classified using the Miettinen risk classes criteria in addition to other risk assessment tools, which categorize them into various risk classes based on their histology, mitotic rate, and other factors. In our study, most patients had low-risk disease similar to the reported series [19].

The coexistence of GIST with other tumors is a complex issue. So far, it has not been established whether the coexistence is stochastic or a result of related pathogenetic mechanisms. Several hypotheses have been proposed to explain the association between GIST and other tumors, including some cancerogenic agents that influence neighboring tissues (e.g., N-methyl-N-nitro-N-nitrosoguanidine-MNNG), and mutations of proto-oncogenes encoding tyrosine kinases such as c-MET. Nevertheless, the available data are insufficient to support any hypothesis [20,21]. Mutations in the succinate dehydrogenase SDH gene and NF-1 gene are believed to be responsible for syndromic GIST such as Carney–Stratakis or Carney triad. In one study, mutations in the KIT gene were found in 62% of patients with GIST and SPM. While PDGFRA mutations were found in 20% [18]. However, this sounds similar to the reported literature of mutations in sporadic GIST without SPM.[22] Hechtman JF et al. conducted a mutational analysis of the KIT/PDGFRA mutations in GIST with SPM for 260 patients from Memorial Sloan Kettering Cancer. They did not detect any relationship between KIT or PDGFRA mutations in GISTs and SPM. Although they found a correlation between KIT exon 11 mutations and subsequent SPM, there was selection bias that limited the generalizability of this finding. Nevertheless, the driver mutation that links GIST with other SPM has not yet been identified.

Little is known about survival outcomes for GIST with SPM. Different studies show that the development of a second malignancy in patients with a history of GIST impact prognosis. A study by Kramer et al showed that 5-yr OS was altered in GIST patients with and without secondary malignancy with a statistically different result of 62.8% and 83.4% [23,24]. In our study, patients who had GIST with SPM had shorter OS compared to patients without SPM 79.8% vs. 94.1%, respectively, (p=0.03). The shorter survival in the SPM group could be driven by the outcome of second malignancies. There are limited data to guide the surveillance of GIST after curative treatment. Rodriquenz et al. suggested that tailored surveillance strategy should be utilized for both GIST and second malignancies. [18] Based on the high incidence of SPM in our study as well as other studies, incorporating surveillance for SPM should become part of GIST management.

Our study has several limitations, including a retrospective design and the lack of mutational analysis data.

Conclusions

We observed that one out of four GIST patients have SPM. Skin, prostate, breast cancers were the most common SPM associated with GIST. More studies are needed to identify the molecular mechanisms by which SPM and GISTs develop. Oncologists should be aware of the possibility of SPM with GIST.

Simple Summary

In the present study, we evaluated the incidence of Second Primary Malignancies (SPM) in patients of Gastrointestinal Stromal Tumors (GISTs). A total of 248 patients with GIST were identified. SPMs were observed in one out of four GIST patients. Skin, prostate, and breast cancers were the most common SPM associated with GIST. The mechanisms underlying the association of GIST with other malignancies need to be explored.

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