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Risk of second primary tumors in GIST survivors: A systematic review and meta-analysis

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ABSTRACT

Introduction: Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors arising in the gastrointestinal tract. Second primary tumors (SPTs) have been reported frequently, either synchronously or during follow-up, in patients diagnosed with GISTs.

Methods: We carried out an electronic search of PubMed, SCOPUS, Web of Science, EMBASE, and the Cochrane Library seeking articles investigating the incidence of SPTs in patients with concomitant GIST. All studies were evaluated for heterogeneity before meta-analysis and for publication bias. Pooled incidence rate was estimated using fixed- and random-effects models. Subsite of SPTs was also investigated.

Results: A total of 32 studies met the inclusion criteria, for a total of 19,627 patients with a diagnosis of GIST. The pooled prevalence of SPTs was 20%, with 14% and 3% being synchronous and metachronous tumors, respectively. We found a risk for several specific cancer sites, in particular gastrointestinal (5%) and genitourinary tract cancers (3%). The most frequently associated malignancies were: colorectal (17%), prostate (14%), gastric (9%), esophageal (5.5%), lung (5.4%), hepato-biliopancreatic (4.7%), breast (4.6%), lymphoma (4.4%), kidney (4.35%), and sarcomas (3.3%). Regression analyses revealed a significant positive association for all SPTs with follow-up and Miettinen risk.

Conclusions: Our results indicate that 20% of patients with GIST experienced a SPT, primarily synchronously with a diagnosis of GIST. In particular, we observed an excess of incident gastrointestinal tumors. These findings have important implications for both pathologists, who should perform extensive molecular analysis of surgical non-GIST specimens in resected patients, and for oncologists, who should continue to follow up GIST patients.

1. Introduction

Patients diagnosed with cancer have an increased risk of developing second primary tumors (SPTs) during their follow-up. Specifically, following the diagnosis of primary breast cancer or lymphoma, there is an increased risk of second breast and non-breast cancers; further, the risk of SPTs is high in childhood cancer survivors or after a diagnosis of either thyroid cancer or melanoma [1–6]. Gastrointestinal stromal tumors (GIST) are c-KIT-expressing mesenchymal neoplasms arising in the gastrointestinal tract wall. Surgery of the primary tumor with negative resection margins is the principal curative option. Post-treatment follow-up is generally recommended and performed to detect potential recurrences, particularly in high risk GISTs, where imaging studies should be protracted up to 10 years after finishing adjuvant therapy [7].

Due to overall improvement of the cures, the rate of long-term GIST survivors has significantly increased in recent years. In parallel, the lifetime risk of developing other malignancies may potentially have risen. In fact, the mean age at diagnosis was 63 years in an analysis of SEER registry data [8], and 66–69 years in two further European population-based series [9,10]. Sub-centimetric GISTs are found incidentally during surgery or follow up for the treatment of other epithelial cancers (e.g., gastric cancer) [11]. Single series and case reports also document the occurrence of synchronous or metachronous SPTs of an epithelial nature (e.g., gastrointestinal cancers), most of which are deemed a simple coincidence. However, gene mutations or the effect of carcinogens on adjacent tissues may be other possible explanations for the

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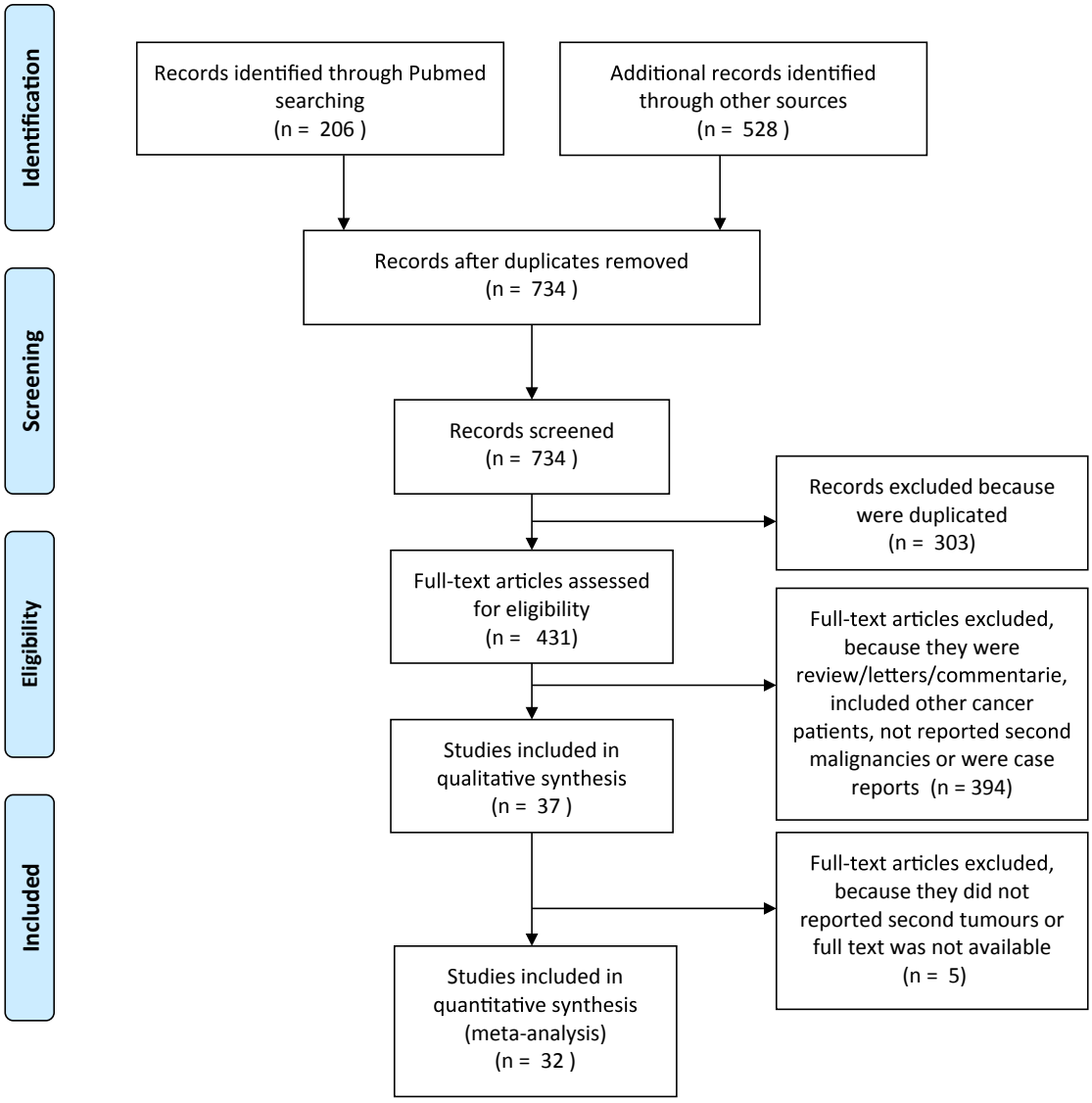

Fig. 1. Flow diagram of included studies.

onset of SPTs. The rate of concomitant SPTs or of those appearing after a diagnosis of GIST is currently unknown due to the sporadicity of cases and to the limited number of published cases. In large cohorts and systematic reviews, the reported risk is about 14–19% [12,13].

Firstly, we carried out a systematic review and meta-analysis to provide a quantitative assessment of the SPT risk in GIST survivors. Secondly, we examined the link between GIST risk factors or other clinical variables and the risk of SPTs. We also aimed to estimate the pooled incidence of SPTs, both overall and for specific tumors.

2. Material and methods

The meta-analysis was carried out in accordance with guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group [14].

2.1. Search strategy

We conducted an electronic search of the literature in the databases of PubMed, SCOPUS, Web of Science, the Cochrane Library and EMBASE. We used the term gist [All Fields] AND ((“neoplasms, second primary” [MeSH Terms] OR (“neoplasms” [All Fields] AND “second” [All Fields] AND “primary” [All Fields]) OR “second primary neoplasms” [All Fields] OR (“second” [All Fields] AND “malignancies” [All Fields]) OR “second malignancies” [All Fields]) OR (second [All Fields] AND primary [All Fields] AND (“tumors” [All Fields] OR “neoplasms” [MeSH Terms] OR “neoplasms” [All Fields] OR “tumors” [All Fields])) OR (“neoplasms, second primary” [MeSH Terms] OR (“neoplasms” [All Fields] AND “second” [All Fields] AND “primary” [All Fields]) OR “second primary neoplasms” [All Fields] OR (“second” [All Fields] AND “neoplasm” [All Fields]) OR “second neoplasm” [All Fields]) OR metachronous [All Fields] OR synchronous [All Fields]). In addition, we reviewed the reference lists of relevant studies to identify additional relevant published articles. Studies were reviewed and data extracted and cross-checked independently by two reviewers (FP and MG); disagreements were resolved by consensus with another author (GT).

2.2. Selection criteria

We included studies that met each of the following criteria: (i) published in the English language between inception up to August 2017; (ii) included patients with newly diagnosed GIST; (iii) investigated the risk for SPTs in GIST survivors; (iv) reported number and sites/type of SPTs or data allowing such outcomes to be derived; and (v) published as full text papers (no abstracts, reviews, commentaries, letters, or editorials). When two or more articles reported duplicate

Table 1a
Characteristic of included studies.

Author/year	Type of study	Observation period	N° pts	Median age (years)	Male/female (%)	Country	Median follow up	Second primary tumors (n) and timing (Synchr/Metachr)
Abdullgaffar/2010	R	(1992–2009)	21	45	0/100	United Arab Emirates	NA	5 (1/4)
Agaimy/2006	R	(1970–1996)	2809	NA	–	Germany + US	NA	258 (NR)
Arnogiannaki/2010	R	(1999–2008)	19	63	40/60	US + Greece	NA	6 (4/2)
Biasco/2009	R	(NR)	172	64.8	50/50	Italy	NA	36 (NR)
Chan/2012	R	(2005–2010)	15	67	70/30	Canada	11	11 (15/0)
D'Ambrosio/2017	R	(2001–2012)	233	NA	–	Italy	68	62 (8/29)*
Du/2016	R	(2009–2014)	286	58	60/40	China	32	47 (47/0)
Ferreira/2010	R	(1998–2006)	43	62	20/80	Brazil	NA	6 (6/0)
Giuliani/2012	R	(2002–2010)	24	NA	50/50	Italy	13	8 (6/2)
Goncalves/2010	R	(1998–2008)	101	68	35/65	Brazil	41	14 (8/2)°
Hechtman/2015	R	(2009–2013)	260	57	–	US	33	50 (5/12)^
Joensuu/2016	Phase 3	(2004–2008)	397	61	–	Europe	90	41 (0/41)
Kover/2004	R	(1991–2004)	43	NA	30/70	Hungary	NA	7 (5/2)
Kramer/2015	R	(2006–2011)	979	68	50/50	Germany	48	503 (NR)
Lai/2016	R	(1995–2015)	749	NA	55/45	Taiwan	NA	136 (64/22)#
Lin/2014	R	(2000–2011)	170	61	76/24	China	38	42 (42/0)
Liszka/2007	R	(1989–2006)	82	60	55/45	Poland	NA	22 (2/18)§
Liu/2009	R	(2000–2007)	54	61	90/10	Japan	NA	54 (54/0)
Liu/2016	R	(2010–2015)	241	58	88/12	China	32	24 (24/0)
Miettinen/2007	R	(1970–1996)	1892	NA	44/66	US	168	9 (0/9)
Murphy/2015	R	(2001–2011)	6112	NA	–	US	NA	1208 (467/71)**
Pandurengan/2010	R	(1995–2007)	783	57	61/39	US	57	186 (0/52)°°
Phan/2013	R	(1992–2009)	1241	NA	57/43	US	NA	90 (NR)
Ponti/2010	R	(1988–2007)	141	NA	44/56	Italy	NA	46 (23/10)##
Richter/2007	R	(1993–2005)	54	65	–	Germany	63	14 (9/5)
Rodriquenz/2016	R	(2002–2014)	128	65	39/61	Italy	49	46 (29/8)§§
Rubio-Casadevall/2015	R	(1996–2006)	132	65	–	Spain	97	22 (11/11)
Sandvik/2010	R	(1980–2009)	52	67	–	Norway	NA	12 (9/3)
Shen/2015	R	(2009–2014)	161	69	70/30	China	21	61 (100/0)
Smith/2016	R	(2001–2009)	1705	63	59/41	Canada	22	181 (65/54/43 both Synchr& Metachr)
Vassos/2014	R	(2000–2009)	86	66	73/27	Germany	60	37 (24/10)***
Zhang/2015	R	(2005–2014)	585	64	50/50	China	32	32 (32/0)

Legend: NR, not reported; R, retrospective; US, United States; * 25 preceded GIST diagnosis; °, 2 cases preceded GIST diagnosis; ^, 33 s tumors preceded GIST diagnosis; #, 50 s tumors preceded GIST diagnosis; §, 2 s tumors preceded GIST diagnosis; **, 651 s cancer preceded GIST diagnosis; °°, 134 s tumors preceded GIST diagnosis; ##, 11 s tumors preceded GIST diagnosis; §§, 9 s tumors preceed GIST diagnosis; ***, 3 tumors preceded GIST diagnosis.

data, we included the most recently updated data or the most informative study. Studies including patients with other sarcomas (e.g., leiomyomas or leiomyosarcomas) were excluded. Papers were also excluded if they did not report the site or the number of SPTs.

2.3. Data extraction

A standardized word form was used for each study included in the meta-analysis. Extracted data included paper characteristics (first author's last name, publication year, median age), study design, number of GIST patients, size/site of GISTs, adjuvant therapy, number of cases observed with SPTs and sites, timing of SPTs (synchronous vs metachronous), and site of GISTs associated with SPTs.

2.4. Statistical analysis

For dichotomous variables, we calculated raw proportions of events (SPTs) divided by the total number of clinically evaluable patients with GIST. The primary endpoint was the prevalence expressed as pooled rate of SPTs (overall rate of SPTs and rates of site-specific SPTs). Incidence of main sites of GIST associated with SPTs was the secondary endpoint. When available from published data or Kaplan-Meier curves, survival of patients with and without SPTs was also compared.

Heterogeneity across studies was evaluated by computing both Q and I^2 statistics [14]. A significant Q value indicated the lack of homogeneity of results among studies, whereas I^2 values of 25, 50 and 75% were defined as low, moderate, and high heterogeneity, respectively [15]. When $P < 0.10$ or $I^2 > 50\%$, a random effects model was used to pool effect sizes of each study for heterogeneity. Alternatively, a fixed effects model was selected. Meta-regression was performed to adjust for specific covariates. Then we conducted publication bias analyses to control for the fact that published studies may present results that differ from those reported in unpublished studies. We examined two publication bias tests for the primary endpoint: the Egger's regression method [16] and the Begg and Mazumdar's rank correlation test [17,18]. In both tests, the absence of publication bias is indicated by non-significant results.

3. Results

3.1. Search results

We initially identified 734 potentially eligible studies (Fig. 1). After exclusion of duplicate references, abstracts, non-relevant literature, and papers that did not satisfy inclusion criteria, 32 candidate articles were included in the meta-analyses (Tables 1a and 1b) for a total of 19,627 patients with a diagnosis of GIST available [12,13,19–49]. All studies were retrospective case series except one that was a phase 3 trial. Patients' numbers ranged from 19 to 6112. The majority were Caucasian series; only 7 studies reported on Asian patients with GIST and SPTs (16% of all SPTs). In 20 studies with data available, clinical presentation of SPTs was, in 60% of cases, incidental (radiological, intra-operatory or pathological finding).

3.2. Risk of SPTs in the overall population of GIST

Overall, the cumulative prevalence rate of SPTs was 20.4% (95%CI 15.9–25.7%) according to the random effect model ($I^2 = 97.7\%$, P for heterogeneity < 0.001). Among 28 studies with available data for site of SPTs, 2414 SPTs were diagnosed in 18,170 GIST patients (Table 2).

Table 1b
Characteristics of primary gastric GIST associated with second primary tumors.

Author/year	GIST primary site (%)	Mean size	Risk category	Clinical presentation (clinical vsRx/path/intraoperatory %)	Adjuvantimatinib
Abdullgaffar/2010	GA 48, SB 24, CRC 10, Extra Ga 19	11.5	High 62, Low 14, Int 24	80/20	NA
Agaimy/2006	NA	NA	NA	99/1	NA
Arnogiannaki/2010	GA 53, SB 37, CRC 5, Om 5	9	NA	20/80	NA
Biasco/2009	GA 56, SB 34 CRC/E/om 10	7	High 25, Low 25, Int 50	–	24
Chan/2012	GA 87, Es 13	NA	Low 93, Very low 7	1/99	0
D'Ambrosio/2017	GA 58, SB 33, CRC 7, Otr 2	NA	High 45, Int 15, Low 22, Very low 18	90/10	0
Du/2016	GA 92, SB 6, Ot 2	NA	High 26, Int 32, Low 22, Very low 20	0/100	49
Ferreira/2010	GA 53, SB 35, CRC 5, Mesentery 7	7.4	NA	0/100	NA
giuliani/2012	NA	NA	NA	0/75	NA
goncalves/2010	GA 57, SB 29, CRC 7, Mesentery 7	4.79	High 14, Int 36, Low/very low 50	40/60	NA
Hechtman/2015	GA 56, SB 38, Es 2, CRC 2, Unknown 2	8.4	High 53, Low 38, Unknown 9	34/66	79
Joensuu/2016	GA 51, SB 34, CRC 9 Es 1, Retroperitoneal 2, Ot 3	9.5	High 33, Low 46, Int 14, NA 7	–	100
Kover/2004	NA	NA	NA	30/70	NA
Kramer/2015	GA 64, SB 29, CRC 5, Ot 2	5.4	High 26, Int 22, Low 34, Very low 18	–	NA
Lai/2016	NA	NA	NA	53/47	NA
Lin/2014	GA 100	NA	High 19, Int 17, Low 34, Very low 30	98/2	31
Liszka/2007	GA 55SB 27, Ot 18	NA	NA	20/80	NA
Liu/2009	GA 63, Es/pancreas/anal 2SB 22, CRC 10, Mesentery/om 3	5.5	Low 90.7, Very low 9.3	0/100	NA
Liu/2016	Proximal 54, Middle 31, Distal 11, NA 4	NA	High 22, Int 24. Low 25, Very low 23, NA 6	90/10	21
Miettinen/2007	GA 59, SB 41	4.5	NA	0/100	0
Murphy/2015	GA 55, SB 29, CRC 6, Peritoneum 2, Ot 6, hepatobiliopancreatic/ retoperiit. 2	NA	NA	–	NA
Pandurengan/2010	GA 49, SB 35, Retroperitoneal 7, CRC 6 Om 2, NA 1	7.5	NA	–	57
Phan/2013	NA	NA	NA	–	73
Ponti/2010	NA	NA	NA	–	NA
Richter/2007	GA 50, SB 39, CRC 4, Es 2, Unknown 5	NA	NA	–	NA
Rodriquenz/2016	GA 59, SB 29, Om 5, CRC 4, Anus/GEJ/vagina 3	5	High 45, Int 30, Low/Very low 25	–	NA
Rubio-Casadevall/2015	GA 58, SB 35, Peritoneum 4, Es 1, CRC 2	NA	High 35, Int 21, Low/Very low 30, NA 14	–	17
Sandvik/2010	GA 58, SB 38, CRC 4	6.6	High 31, Int 19, Low 21, Very low 27, NA 2	25/75	NA
Shen/2015	GA 83, SB 11, Ot 6	NA	High 31, Int 16, Low 17, Very low 36	0/95	NA
Smith/2016	GA53, CRC 5, SB 28, Soft/connective 5, Ot 9	NA	NA	–	NA
Vassos/2014	GA 65, SB 32, Es 2, CRC 2	2.2	None 68, Int 16, Low 3, Very low 11, Other 2	–	3
Zhang/2015	NA	NA	NA	12/88	1

Legend: CRC, colorectal; Es: esophagus; GA, gastric; Int, intermediate risk; NA, not available; Om: omentum; Ot: other SB: small bowel.

Table 2
Frequence of second tumors in GIST survivors according to site.

Second primary tumors	Subsite	Rate of SPTs: n (%) cases/ n°pts	Incidence % cases/n°SPTs
Gastrointestinal	Esophagus	133 (0.7)	5.5
	Stomach	223 (1.2)	9.2
	Colorectal + appendix	415 (2.2)	17
	Hepatobiliopancreatic	115 (0.6)	4.7
	Small bowel	12 (0.06)	0.49
	Not specified	7 (0.038)	0.27
	Other	18 (0.1)	0.74
	Subtotal	**923 (5%)**	**37.9**
Genitourinary	Prostate	341 (1.87)	14.1
	Kidney	105 (0.57)	4.35
	Bladder + other urothelial tract	66 (0.36)	2.73
	Testicular	9 (0.05)	0.37
	Not specified	21 (0.11)	0.87
	Subtotal	**542 (3%)**	**22.4**
Gynaecologic	Site not specified	27 (0.14)	1.1
	Utherine	40 (0.22)	1.65
	Ovary	18 (0.09)	0.74
	Other	6 (0.03)	0.25
	Subtotal	**91 (0.48)**	**3.74**
Thoracic	Lung	132 (0.72)	5.4
	Mesothelioma	1 (0.005)	0.4
	Not specified	1 (0.005)	0.4
Subtotal	**Subtotal**	**134 (0.73)**	**6.2**
Breast	Breast	111 (0.61)	**4.6**
Skin	MM	89 (0.49)	3.68
	Other skin cancer	23 (0.12)	0.95
	Subtotal	**112 (0.61)**	**4.63**
CNS	Brain	9 (0.049)	0.37
	Uveal melanoma	1 (0.005)	0.04
	Other	3 (0.016)	0.12
	Subtotal	**13 (0.07)**	**0.53**
Hematologic	Myeloma	8 (0.04)	0.33
	Lymphomas	107 (0.59)	4.4
	Leukemia	32 (0.17)	1.3
	Other	6 (0.03)	0.25
	Subtotal	**153 (0.84)**	**6.28**
Other	Head & neck	18 (0.1)	0.74
	Sarcoma (bone + STS)	80 (0.4)	3.3
	GIST	1 (0.005)	0.04
	Carcinoid/neuroendocrine	60 (0.3)	2.48
	Cancer of unknown primary	10 (0.05)	0.4
	Thyroid	46 (0.25)	1.9
	Paraganglioma/ neuroblastoma/ pheocromocytoma/adrenal	9 (0.05)	0.37
	Not specified	7 (0.038)	0.29
	Subtotal	**231 (1.27)**	**9.52**
Benign tumors	Various histologies	29 (0.16)	**1.2**
Cancer not-specified	Unknown primary or not	75 (0.41)	**3.1**
Total all sites (cumulative incidence rate)		**2414/ 18,170 (13.2)**	**100**

Table 3
Site of GIST with associated second primary tumors.

Site of GIST	N° of SPT	N° of pts	% of pts with SPT
Gastro-esophageal	717	687	67.2
Small intestinal	212	200	19.8
Colorectal	30	30	2.8
Other sites	22	22	2
Site-not specified	85	85	7.9
TOTAL	1066	1024	100

SPT, second primary tumors.

The two main anatomic sites of origin of SPTs were gastrointestinal and male genitourinary cancers (5 and 3%, respectively). Other tumors frequently observed were hematologic and thoracic cancers (both about 1%). The category "others," including rare tumors, sarcomas, endocrine, and head & neck malignancies, accounted for 1.27% of the incidence. Among 16,892 patients with data available for timing of SPTs, 14.6 and 3.35% had synchronous and metachronous SPTs, respectively. A SPT preceded the diagnosis of GIST in 4.6% of cases.

3.3. Incidence of SPTs according to anatomic sites

Among solid tumors and hematological malignancies diagnosed in patients with a history of GIST, the most frequent were gastrointestinal (37.9%) and genitourinary cancers (22.4%), which accounted for 60% of all SPTs (Table 2). Different types of SPTs were classified as "others" and included sarcoma/endocrine/rare tumors and head & neck, thoracic, breast, skin, hematological, gynecologic, central nervous system, benign tumors, and cancers with an unknown primary. The most frequent malignancies (with an incidence higher than 3%) were colorectal (17%), prostate (14%), gastric (9%), esophageal (5.5%), lung (5.4%), hepatobiliopancreatic (4.7%), kidney (4.35%), breast (4.6%), lymphoma (4.4%) and sarcomas (3.3%). Primary sites of GIST were the stomach and the small bowel, in 67 and 19.8% of cases, respectively (Table 3).

3.4. Sensitivity analysis

Prevalence rate was adjusted as a function of median age, median follow up, mean size and class risk of GIST, and adjuvant therapy with imatinib. The only variables associated with greater risk of GIST were shorter follow up ($P = 0.0008$) and high risk according to Miettinen classification ($P = 0.04$).

Publication bias was not evident when the Begg and the Egger tests were used.

4. Discussion

GISTs are relatively rare neoplasms affecting the gastrointestinal (GI) tract and arising from the muscular wall of viscera. Despite being the most common of the non-epithelial neoplasms involving the GI tract, mesenchymal tumors account for only 1% of primary GI cancers [50,51]. GISTs occur predominantly in middle-aged and elderly subjects, and rarely in patients younger than 40 years. Such tumors are generally managed with surgery, followed by adjuvant therapy for high-risk patients. In this specific setting, excellent 5-year survival rates are normally registered, approaching 80–90% in patients receiving 1–3 years of adjuvant imatinib [29].

To our knowledge, this is the first systematic review and pooled analysis collecting the burden of data and the specific subsites of SPTs in patients with GIST. The search was extensive and included both retrospective and prospective cohort series and clinical trials, for a total of more than 19,000 patients with GIST.

A 20% rate of GIST survivors developed a synchronous (14%) or metachronous (3%) epithelial or hematological cancer, with more rare cancers such as sarcomas being very infrequent (< 0.5%). In 4% of cases, a SPT preceded the diagnosis of a GIST. The risk of SPTs was not a late event in the natural history of GIST. Indeed, 85% of SPTs either preceded or were synchronous with stromal tumors. In the other cases, small GISTs were an incidental finding during specimens' assessment of cancers of different origin. According to the anatomic site, 60% of SPTs arose from gastrointestinal and male genitourinary tracts (incidence of 38 and 22%, respectively); the other STPs had an incidence lower than 1%, except for rare tumors showing a cumulative incidence rate of 1.17% (about 9% of the total SPTs). Sex distribution was very similar, and clinical presentation (with symptoms or signs) was more common in SPTs that preceded or followed primary GIST. Conversely, most synchronous SPTs were incidentally found during pathological examination or during imaging work-up for primary GIST staging, and were gastrointestinal carcinomas or benign tumors.

We indirectly compared the incidence of SPTs in this GIST population with the cases of expected cancers in the United States (US) in 2018, which were recently reported [52]. Among non-hematological

malignancies, rates of gastrointestinal tumors appear almost double as compared to US registries (38 vs 18%). Also, about 2- and 3-fold less risk of thoracic and breast cancers were observed in our series (5 vs 15, and 14%, respectively). Cancer frequency in Europe in 2012 was similar, with 24% of gastrointestinal tumors among all cancer sites, and 13 and 12% of breast and lung cancers, respectively [53]. One possible explanation may be the same anatomic district or chance in the first case, and less common smoking habits (not a risk factor for GIST) or different age distribution between the sexes in our analysis, in the second case (median age of GIST cases was 63 years). It is well known that breast and lung cancer incidence rises with age. An abdominal directed follow up is usually pursued in GIST patients, and this could have increased the probability of diagnosing new incident (gastrointestinal) carcinomas. Compared to the mentioned statistics, a similar frequency of genitourinary cancers and hematological neoplasms were finally observed.

The biological plausibility that links the history of GIST to SPTs of different origin is currently unknown. Second or multiple tumors are frequently described in cancer survivors, and the main reasons often include a common etiology (e.g., smoke or sunlight exposure for upper aerodigestive or non-melanoma skin cancers), previous history of breast cancer (e.g., for contralateral breast tumors), the iatrogenic effect of treatments (e.g., chemotherapy and/or radiotherapy in the case of breast cancer in lymphoma survivors) or genetic causes in familial syndromes. An analysis from the Italian AIRTUM tumor registry calculated a 10% increase in the risk ratio in observed/expected second tumors in patients with a previous diagnosis of cancer [54]. In the same study, the cumulative proportional 10-year rates were 6 and 10% for female and male patients, respectively. However, some hypotheses can be advanced to explain the occurrence of SPTs. GISTs synchronous with GI tract neoplasms (70% of the total cases found) are mostly found incidentally during a planned surgery for symptomatic carcinomas. It is estimated that the frequency of incidentally detected sub centimetric gastric GIST lesions might be much higher than previously expected but, given the relatively low annual incidence of clinical GISTs, only a few microscopic tumors may enlarge and become clinically relevant in size and with malignant potential. Thus, similar cases are incidentally discovered when other more aggressive tumors such as gastric carcinomas become apparent [55].

As for metachronous SPTs (15% of the total cases found), the correlation with a previous GIST is somewhat difficult to interpret. One hypothesis is the independent risk to develop cancer due to increasing age and obvious implications associated with a longer exposure to cancerogenic agents. Second, c-KIT cancerogenesis could be implicated both in solid and hematological malignancies (e.g., melanoma and acute myeloid leukemias) [56]. Third, the influence on the hematopoietic response by imatinib treatment may reduce the immune-surveillance and lead to an increased potential risk of SPTs. Indeed, in addition to targeting tumoral c-KIT oncogene products, imatinib modulates tyrosine kinases involved in both effector and regulatory immune cells implicated in cancer surveillance [57]. Phan et al., who analyzed the SEER database from 1992 to 2009, found a significant increased risk of SPTs (mainly kidney and colorectal cancer) following the introduction of imatinib in 2002 (7% vs 1% in post- vs pre-imatinib era, respectively) [49]. The higher incidence of SPTs in the post-imatinib era may also be secondary to the improved surveillance of primary GISTs with clinical and radiological imaging tests and prolonged survival of patients after the introduction of targeted therapies.

However, some questions remain unanswered. Specifically, is GIST prognosis affected by the occurrence of a SPT? Additionally, is the outcome of a SPT different in the case of history of a previous GIST? Kramer et al. found that 5-year survival was 62.8% and 83%, respectively, in patients with and without the diagnosis of a SPT [30]. Similarly, Liu et al. reported 5-year disease-specific survival rates for gastric GIST with and without synchronous gastric cancer of 37.9% vs 89.9%, respectively [34]. Due to insufficient data, a survival analysis could not be performed in the present meta-analysis.

This analysis has obvious limitations. First, this is not an individual patient data meta-analysis and therefore, the characteristics of patients developing SPTs are not known (age, comorbidities or specific risk factors). Second, we did not search for unpublished studies, case reports, and publications in non-English languages. Third, we observed considerable heterogeneity among studies due to study design (cancer registries vs single institution series), SPTs histology, period of recruitment, duration of follow-up, geographical and genetic variables, and treatments used, but we were unable to account for all these variables. Ultimately, we were not able to calculate the outcome of SPTs to evaluate if survival of these patients differs from that of sporadic cancers with similar histology but no previous history of GIST.

In conclusion, we report that GIST patients experienced a 20% overall risk for both synchronous (85%) and metachronous (15%) tumors of different histology. Most SPTs were incidentally found during radiological staging of GIST, at time of surgery, or at final pathological examination. In particular, for currently unknown reasons, there seems to be an excess of gastrointestinal tumors compared with the general population. The high rate of synchronous GISTs and SPTs may imply a more extensive pathologic evaluation of surgical specimens. In particular, testing for molecular pathway aberrations commonly observed in GIST (e.g. KIT and PDGFR gene mutations) should be performed in order to understand a possible relation with the development of a SPT, especially in those treated with specific tyrosine kinase inhibitors. Hechtman et al. found that patients who developed other malignancies after GIST more often had KIT exon 11 mutations (100 vs. 66%, $P = 0.01$) [13]. The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) play also a key role in signaling pathways in oncogenesis and/or pathological presentation in both GIST and gastric/colorectal cancers [58,59].

Finally, since surveillance is usually tailored according to the risk of recurrence, findings from our work may suggest that follow-up of patients diagnosed with high risk GISTs should not be suspended early in order to detect eventual relapses or second primary malignancies.

Conflicts of interest

None.

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