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Review

Additional primary malignancies in patients with gastrointestinal stromal tumors. Proposal for a new classification☆

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ABSTRACT

Additional primary malignancies in patients with gastrointestinal stromal tumour (GIST) is not only common but of growing interest in the scientific literature. This association is of great importance in terms of clinical challenge, diagnosis and therapy as well as for the prognosis impact it implies. In the published series there is a tendency to group these patients to determine the specific and distinguishable characteristics of GIST associated with other malignancies. On the other hand, there is no general consensus or unified classification. This classification would be of great interest, as it would unify criteria, agree groups to compare different series and demonstrate whether the aetiology underlying both tumours and the GIST's own characteristics really vary according to the type in question. We undertook a medical literature review and proposed a new classification for patients with GIST associated with other tumours.

Asociación de tumores del estroma gastrointestinal con otros tumores primarios. Propuesta de una nueva clasificación

Palabras clave:
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RESUMEN

La asociación de *gastrointestinal stromal tumor* (GIST, «tumor del estroma gastrointestinal») con otras neoplasias primarias en un mismo paciente es un hecho no solo frecuente, sino con un interés creciente en la literatura científica. Esta asociación tiene una enorme importancia tanto por el desafío clínico, diagnóstico y terapéutico como por el impacto pronóstico que implica. En las series publicadas existe una tendencia a agrupar a estos pacientes para determinar que los GIST asociados a otras neoplasias tienen características concretas y diferenciables. Por el contrario, no existe un consenso general ni una clasificación unificada. Esta clasificación sería de gran interés, pues permitiría unificar criterios, consensuar los grupos para comparar las distintas series y demostrar si realmente la etiopatogenia subyacente a ambos tumores y las características del propio GIST varían según el tipo de que se trate. Realizamos una revisión de la literatura médica actual y una propuesta de nueva clasificación para pacientes con GIST asociados a otros tumores.

Leaving aside the three known syndromes in which the *gastrointestinal stromal tumours* (GISTs) are associated with other tumours (type 1 neurofibromatosis,[1–3] Carney triad[4,5] and the familial GIST[6,7]), most GISTs develop in isolation and are not associated with other tumour types. But there is a significant percentage of patients with GIST who also develop other primary malignancies (either being diagnosed of GIST first and then the other tumour, or vice versa, and, in both cases, synchronous and metachronous). This association of GIST to other neoplasms has a very significant and growing interest in the scientific literature in recent years. There is no consensus classification of this group of patients, which makes it difficult to analyse in depth the specific characteristics of the groups and to compare different series homogeneously. This would be of great importance, because the underlying aetiology of this association, the type of associated

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Table 1
Main series of patients with gastrointestinal stromal tumours and associated tumours.

Author, reference and year	Origin	n	Cases	%	Most frequent types (%)
Agaimy et al.,[8] 2006	Medical literature review, AFIP, Nuremberg	4777	444	9.3	Colorectal cancer (22) Gastric cancer (19)
Murphy et al.,[9] 2015	SEER	6112	1047	17.1	Genitourinary cancer (35.8) Gastrointestinal cancer (17.2)
Kramer et al.,[10] 2015	Ulm registration	836	422	31.9	Colorectal cancer (21.5) Gynaecologic cancer (19.2)
Hechtman et al.,[11] 2015	MSKCC	260	50	19.2	Genitourinary cancer (44)
Pandurengan et al.,[12] 2010	MDACC	783	159	20.3	Colorectal cancer (9.7) Urological cancer (9.7)
Total		12,768	2122	16.6	

AFIP: Armed Forces Institute of Pathology; GIST: gastrointestinal stromal tumour; MDACC: MD Anderson Cancer Center; MSKCC: Memorial Sloan Kettering Cancer Center; SEER: Surveillance Epidemiology and End Results program; %: percentage of cases with associated tumours.

tumour and the very characteristics of the GIST vary according to each group.

Incidence and associated tumour types

While a decade ago the association of GIST with other malignancies was considered somewhat anecdotal, rare and with few published series, in recent years, the articles that talk about this association have increased in frequency. The reported incidence in the available medical literature of this association is very variable and even contradictory, with figures ranging between 4.5 and 62%.[8,10,13–16] In series like Agaimy et al., the diagnosis of GIST first and then the other neoplasm (31 vs 18% in reverse) is more frequent, being the synchronous diagnosis of both the most common occurrence.[8] Other authors, like Kramer et al.,[10] describe just the opposite, i.e., that diagnosis of GIST is most common in patients with another prior neoplasm (62 vs 44% in the opposite case). Table 1 lists the five most important series, noting that the incidence varies between 9 and 32%, with an average of 16.6%. Based on data from the *Surveillance Epidemiology and End Results* program of the *National Cancer Institute* in the USA on more than 6000 patients,[9] it is estimated that those with GIST a 44% increased prevalence of having developed another tumour before GIST and up to 66% increase in the relative risk of developing another tumour after diagnosis of GIST. We must emphasize that the published data suffer from significant biases, for example, the series include tumours both benign and malignant. Thus, in a review of the GIST Registry of the German city of Ulm,[10] when only malignant tumours were included, the incidence was 32%, but when benign tumours were also included, it reached 50%. Moreover, there may be a bias related to the diagnostic criteria used for GIST, especially in the older series. The type of hospital where the series originates is a source of bias, because there is enormous variability between different centres on the type of patients they treat, the type of complementary examinations, and the number of the same.[17] Finally, the detection rate will depend on the thoroughness of the pathological examination: since most are incidental GIST are gastric and <1 cm, sections for pathological study >1 cm may leave a significant percentage of tumours undiagnosed.[18]

The medical literature identifies gastrointestinal carcinomas, especially colon and stomach, as the most common (47% of gastrointestinal tumours in general, 22% of colon and 19% gastric), followed by those of genitourinary origin (15%).[8] These data vary when we consider the type of temporal relationship between GIST and other neoplasms and the relative frequency of the associated tumour in the general population. It is estimated that the increased risk rate of developing another malignancy in patients with a prior GIST is 8.72 for ovarian carcinoma, 5.89 for adenocarcinoma of the small intestine, 6 for other female genitourinary malignancies and 5.1 in the case of papillary thyroid carcinoma. In patients where GIST is diagnosed during follow-up of a prior primary tumour, increased prevalence rate was 12 for oesophageal adenocarcinoma, 7.5 for bladder carcinoma and 6.1 for any type sarcoma.[9] When we analyse the same data from the point of view of absolute frequencies, we see that in both cases (prior GIST or other prior neoplasm) gastrointestinal tumours (14 and 13.3%, respectively) and genitourinary tumours (14 and 26%, respectively)[9] predominate. In addition to solid tumours, haematological neoplasms associated with GIST; in particular, myeloid leukemias (acute and chronic) and myeloproliferative neoplasms[19] can also be detected.

Etiopathogeny

It is well known that cancer survivors have an increased risk to have a second neoplasm[19] compared to non-cancer population. There are several hypotheses about this tumour association: aetiological molecular pathways common to both tumours, treatment side effects, or just coincidence and better diagnosis due to an increased exposure to diagnostic tests and increased survival of these patients.[19]

There are, in turn, two critical factors that increase the risk of second cancers: survival related to the first tumour, because extended survival times also mean more time for a second neoplasm to develop; and the detection bias in relation to the greater and better control and monitoring of these patients.[20] As we shall see, all these factors have been considered in GIST, and the controversy has narrowed down to finding out whether the origins of this association are a mere coincidence coupled with better diagnostic capabilities, or secondary to a common aetiologic problem between the two tumours.[17,21]

The problem of detection bias is clear and independent of the type of association. That is, both, in the cases of prior GIST, as well as in cases of other tumours prior to GIST, both groups of patients may have been diagnosed by the better and more comprehensive monitoring of these patients.[21] Similarly, in cases where both neoplasms are diagnosed synchronously, this can be the result of a better detection capability, both pre- as well as intra-operatively. This would explain why this subgroup of synchronous neoplasms is the most frequent (up 72.7% in some series[22]).

The hypothesis of coincidence and the best detection is based primarily on two facts: the high incidence of small gastric GISTs and the high average age.

- There is a relationship between patients with GIST associated with other tumour and the fact that GIST is asymptomatic. In most cases, GISTs associated with other tumours are incidental and small (up to 73% < 5 cm),[9,21] in clear contrast with non-associated GISTs, which are greater in size, cause pain or gastrointestinal bleeding.[22,23] Considering the high frequency of gastric micro-GISTs (up to 10% of oesophageal surgery[24] 35% of gastric cancer