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Review

Gastrointestinal stromal tumour and second tumours: A literature review☆

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ABSTRACT

There are several tumours associated with gastrointestinal stromal tumour (GIST), most of them without an apparent family relationship; only 5% of them occur within the context of a family syndrome. In this article the corresponding literature about the former has been reviewed. A search in Pubmed was carried out, the methodology of which is described in detail in the body of the article.

A total of 88 articles have been chosen for the review, next to the application of limits as well as a manual review. GIST patients have a twofold risk of developing a second tumour than the general population (4–33% of them develop a second neoplasm, either synchronic or metachronic). Most incident tumours associated with GIST are gastrointestinal and genitourinary tumours. In addition, patients with second tumours have a worse survival rate than those without second tumours.

El tumor del estroma gastrointestinal y la aparición de segundos tumores: revisión de la bibliografía

Palabras clave:
Tumor del estroma gastrointestinal
Segundos tumores
Segundo primario metacrónico
Neoplasia sincrónica

RESUMEN

Existen una serie de tumores asociados al *gastrointestinal stromal tumour* (GIST, «tumor del estroma gastrointestinal»), la mayoría de los cuales ocurren sin una aparente relación familiar; solo un 5% suceden en el contexto de síndromes familiares. En este artículo se ha revisado la literatura médica existente sobre los primeros. Se ha elaborado una búsqueda en Pubmed cuya metodología se concreta en el cuerpo del artículo.

Han sido seleccionados para la revisión un total de 88 artículos tras la aplicación de límites y revisión manual. Los pacientes con GIST tienen un riesgo aproximadamente 2 veces mayor que la población general de desarrollar otro tumor (4–33% de ellos desarrollan una segunda neoplasia, ya sea sincrónica o metacrónica). Los tumores más frecuentemente asociados son los de origen gastrointestinal y genitourinario. Además, los pacientes con segundos tumores tienen una supervivencia peor que aquellos que padecen únicamente un GIST.

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Introduction

Gastrointestinal stromal tumour (GIST) is a neoplasm derived mainly from the interstitial cells of Cajal, located in the digestive tract wall. It represents 1% of the sarcomas, and about 3–5% of the gastrointestinal tumours, with sarcoma of digestive origin being the one with the highest frequency.

Although its occurrence is typically sporadic, it is estimated that there is a familial association in approximately 5% of cases. Some syndromes have been described as closely associated with the occurrence of the said tumour: neurofibromatosis type 1, familial GIST syndrome, Carney's tetrad and Carney–Stratakis syndrome.

The occurrence and development, at the beginning of the century, of the tyrosine kinase inhibitor imatinib has made the specific treatment of these patients possible, achieving amazing responses in many of them, even extending the life of patients with metastases by many years. This increase in survival has allowed a longer follow-up and monitoring of these patients.

From the late 1990s onwards, some case reports in the medical literature started to show associations with other neoplasms within the same GIST patient, associations that had not been noticed until then. As a result of these publications, the idea that second neoplasms may occur more frequently in patients with GIST than in the general population started to take shape. Throughout the current century, several institutions have published their series of hundreds of patients showing cumulative incidences greater than those expected for the general population. In recent years, several authors have compiled all this information in the form of exhaustive medical literature reviews with the aim of attempting to create an ever-widening "body of science" on this subject.

As far as it has been known, there is no review in Spanish on this subject in the medical literature. The objective of this article is to develop a review of the medical literature to date on the occurrence of second neoplasms in patients with GIST.

Methods

The study is based on an exhaustive literature search in the Pubmed database. The selection of this tool has been based on the fact that its multidisciplinary and international essence allows the availability of sufficient study material for the preparation of this review.

In order to select the study population, a search strategy has been carried out to retrieve all documents published in English, related to GIST and second tumours during the period between 2000 and August 2016, eliminating everything related to tumours occurring in the context of familial syndromes, because they do not meet this study's selection criteria.

To build the search algorithm, a list of terms has been prepared considering both synonyms and related terms in order to give the search the maximum sensitivity. The hierarchical structure of MesH has been revised for the selection of terms and synonyms.

The search was done through free text to retrieve both the indexed documents (included in Medline) as well as those that are in the process of being indexed which would be lost in a controlled vocabulary search, as no MesH terms are yet available.

The terms used were as follows: GIST, GISTs, *Gastrointestinal Stromal Neoplasms*, *Gastrointestinal Stromal Tumour*, *Neoplasm*, *Second Primary*, *Metachronous Second Primary*, *Synchronous Neoplasm*, *Neoplasms*, *Synchronous Multiple Primary Neoplasms*, *Second Primary Cancer*, *Second Cancers* and *Second Tumours*.

To limit the results, the filters provided by the system have been used for date of publication and language.

The total number of documents recovered was 345, of which, after a thorough manual review by title and summary, 88 were chosen for definitive use in the study material of this review.

Results

The first publication on the association between GIST and other tumours was found in 2000: Maiorana et al. describe 6 cases of patients with gastric carcinomas and synchronous GIST.[1]

In 2004, Kalmár et al. published their data on 23 GIST patients, finding other associated tumours in 5 of them, and concluding the existence of a higher rate of neoplasms among patients with GIST compared to the normal population in Hungary.[2] In the same year, Ruka et al. described 18 cases (10%) out of a total of 180 patients with GIST.[3]

Since then, there have been numerous publications in the medical literature in the form of case reports, associating GIST to the occurrence of melanoma in the same patient[4,5]; gastric carcinoma[6–8]; neuroendocrine tumor[9–11]; colorectal cancer[12–17]; oesophagus cancer[18]; PEComa[19]; hepatocarcinoma[20,21]; acute leukemia[22–24]; ovarian cancer[25,26]; pancreatic cancer[27]; lung cancer[28–30]; cholangiocarcinoma[23,31]; kidney cancer[32,33]; breast carcinoma[17]; Merkel cell carcinoma[34]; breast sarcoma[35]; adrenal carcinoma.[36]

Publications with large patient series (some of more than 500 patients) have started to emerge within the last 10 years, allowing to draw conclusions of greater scientific consistency.

In 2009 Liu et al. published their series of 311 patients with GIST, finding secondary tumours of the digestive system in 54 (17.4%) of them.[37] Of particular interest is the small size of incidental GISTs, as well as up to 90% of them were of very low risk, whereas among the symptomatic GISTs (diagnosed through signs and symptoms), the percentage of very low risk was only 1.9%.

Pandurengan et al. found a total of 153 cases (20%) among the 783 GIST patients in their series.[38] Carcinomas of urothelial (8%) and gastrointestinal (6%) origin were especially noteworthy.

Gonçalves et al. collected a total of 14 cases (14%) in a series of 101 patients with GIST,[39] with carcinomas of gastrointestinal origin being the most frequent (57% of second tumours).

Chan et al. analyzed the pathological anatomy of 207 patients who underwent an oesophagectomy or gastrectomy due to epithelial tumours and found a total of 15 GISTs in the surgical specimens.[40]

In the *Memorial Sloan Kettering Center* series published in 2015, Hechtman et al. describe a total of 50 cases of second tumours (19%) out of a total of 260 patients with GIST.[41] In their study, the distinction between second tumours emerging before and after diagnosis of GIST, with subsequent analysis, should be highlighted. Gastric tumours as well as breast and prostate carcinomas were among the most frequent second tumours.

The publication of Giuliani and Bonetti[42] is also from 2015. It is based on 440 patients with GIST, among whom they found second tumours in 64 of them (14.5%); with gastrointestinal carcinomas being the most frequent (47%) followed by carcinomas of genitourinary origin (15%).

In a Spanish study published within the last year, Rubio-Casadevall et al. analyzed a cohort of 132 patients with GIST, finding 30 patients (22.8%) who developed at least one second tumor,[43] with a 2.47 HR of developing a second tumour among patients with GIST.