GASTROINTESTINAL STROMAL TUMORS

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(سَنُرِيهِمْ آيَاتِنَا فِي الْآفَاقِ وَفِي أَنفُسِهِمْ حَتَّى يَتَبَيَّنَ لَهُمْ أَنَّهُ الْحَقُّ)

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Aim of the work

The aim of this work is to provide a review of literature about the anatomical, histological, pathological consideration of gastrointestinal stromal tumors and, its management.

Abbreviations

BID	Twice daily
CML	Chronic myeloid leukemia OR Chronic myelogenous leukemia
CB	Clinical benefit
CR	Complete response
CGH	Comparative genomic hybridization
DFS	Disease free survival
EUS	Endoscopic ultrasonography
GANTs	Gastrointestinal autonomic tumors
GI	Gastrointestinal
GIT	Gastrointestinal tract
GISTs	Gastrointestinal stromal tumors
GIST/Ls	Gastrointestinal stromal tumors and leiomyomas
GIPACTs	Gastrointestinal pacemaker cell tumors
JM	Juxtamembrane
HAE	Hepatic arterial embolization
HPF	High power field
HTERT	Human telomerase reverse transcriptase
HTR	Human telomerase RNA component

IM	Imatinib Mesylate
ICCs	Interstitial cells of Cajal
LMP	Low malignant potential
MVD	Microvessel density
OD	Once daily
OS	Overall survival
PD	Progressive disease
PR	Partial response
PFS	Progression-free survival
PDGFRα	Platelet-derived growth factor receptor alpha
PFS	Progression-free survival
RR	Response rate
SD	Stable disease
SMemb	Embryonic isoform of myosin heavy chain
SMA	Smooth muscle actin
SU	Sunitinib
SUVmax	Maximum standardized uptake value
TAP1	Telomerase-associated protein 1
VEGFRs	Vascular endothelial growth factor receptors

CONTENTS

LIST OF FIGURES

INTRODUCTION

AND HISTORICAL BACKGROUND

OF GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract. **"S. Hinz, et al., 2006"**

Mesenchymal tumors are a family of related tumors including those named plexosarcomas, leiomyoblastomas, leiomyosarcomas, GISTs, gastrointestinal autonomic tumors (GANTs), and gastrointestinal pacemaker cell tumors (GIPACTs). **"Megan M. D., et al., 2004"**

The first accurate description of mesenchymal neoplasms of the gastrointestinal tract (GIT) was in 1941. Traditionally, these tumors were thought to be derived from smooth muscle cells, based on their resemblance to smooth muscle tumors and they were designated as leiomyomas, bizarre leiomyomas, cellular leiomyomas and leiomyosarcomas. However, with the advent of electron microscopy, it has been shown that relatively few neoplasms showed convincing ultrastructural evidence of smooth muscle differentiation. The application of immunohistochemistry revealed that many of these neoplasms lacked the immunophenotypical features of smooth muscle differentiation. **"Muna S., et al., 2005"**

The term Gastrointestinal stromal tumors (GISTs) was first used by Mazur and Clark in 1983, and includes a heterogeneous group of nonepithelial neoplasms with spindle or epithelioid cells, which may display myogenic features (smooth muscle GISTs), neural attributes (gastrointestinal anatomic nerve tumor), or characteristics of both muscle and nerve (mixed GISTs), or may lack differentiation (GISTs not otherwise specified). **"Nikolaos K., et al., 2005"**

Subsequently, Herrera et al. introduced the concept of 'plexosarcoma' in 1984 to acknowledge the existence of a small subset of stromal tumors with autonomic neuronal differentiation which became better known as gastrointestinal autonomic nerve tumors (GANTs**). "Muna S., et al., 2005"**

With the advent of immunohistochemical analysis allowed the definition of a new entity among the gastrointestinal mesenchymal tumors: the gastrointestinal stromal tumors (GISTs) which particularly express the c-kit (CD117) protein a growth factor trans-membrane receptor with tyrosine kinase activity. **"Daniel V., et al., 2005"**

They may occur anywhere along the length of the digestive tract from the esophagus to the anus. They account for approximately 1–3% of gastric neoplasms, 20% of small bowel tumors and 0.2–1% of colorectal tumors. Approximately 60–70% of the GISTs arise in the stomach, 20–30% in the small intestine, 5% in the colon and in the rectum, less than 5% in the esophagus and Sometimes develop outside the intestinal tract, in the abdominal cavity. **"Nikolaos K., et al., 2005"**

There was considerable controversy as to the line of differentiation, since some tumors exhibited a myogenic phenotype, others showed neural differentiation, some revealed mixed differentiation and some cases did not show any specific line of differentiation, the 'null phenotype'. **"Muna S., et al., 2005"**

Rosai (1996) divided GISTs into four major types: smooth muscle; neural; combined smooth muscle-neural; and uncommitted. Recent studies have reported GIST cells demonstrating characteristics similar to those of the interstitial cells of Cajal (ICC), or 'pacemaker cells', which play a neuromotor role in normal gut motility. **"Ken-ichi M., et al, 2006"**

GISTs also vary greatly in size, morphology, and malignancy potential, creating a continuum of neoplasms with uncertain malignancy potential ranging from virtually benign tumors to overtly malignant, aggressive cancers. The more indolent GISTs are typically small, sometimes incidentally found tumors that might not have surfaced during the lifetime of a patient, whereas other GISTs may present with overt metastases already at the time of the diagnosis**. "Heikki J., 2006"**

GISTs typically arise in the bowel wall, usually from the muscularis propria, and may extend intra- or extraluminally**. "P.J. O'Sullivan, et al., 2006"**

GISTs arise from activating mutations in KIT or platelet-derived growth factor receptors α (PDGFRα). **"Michael C. H., 2006"**

Immunohistochemically, the tumor cells revealed a phenotype similar to Cajal cells, occasionally with differentiation to smooth muscle cells or neural cells. Non-epithelial tumors originating from the gallbladder are rare. Among these, rhabdomyosarcoma, malignant fibrous histiocytoma, and angiosarcoma reportedly represent malignant mesenchymal tumors. **"Makoto F., et al., 2005"**

Risk factors and aetiology are unknown, but there is said to be a rare association with neurofibromatosis type. Some studies show no significant sex difference, whilst others show a male predominance. Most GISTs occur in older patients, typically between the ages of 50–60. Sporadic instances are rare before the age of forty. However, GISTs can be familial, thus can be present in younger patients. **"P.J. O'Sullivan, et al., 2006"**

Primary GISTs may occur in locations other than gastrointestinal tract for example the first case of a large Primary gastrointestinal stromal tumor presenting as a uterine mass in a 77-year-old female. It is extremely rare that these tumors occur in the bile tract, and only a few cases have been reported. **"Makoto F., et al., 2005"**

It is generally accepted that the criteria needed for predicting biological behavior may differ significantly with location. For example, in the colon, size smaller than 2 cm and mitotic rate less than 1 mitosis / 50 HPF are indicators of benignity, while size larger than 5 cm and mitotic rate greater than 5/10 are generally accepted as predictors of malignancy. **"Hillemanns M., et al., 1998"**

This lack of clarity in distinguishing GISTs can potentially affect clinical decision-making, because non-GISTs included in the differential diagnosis are sensitive to systemic chemotherapeutic treatment, whereas GISTs is resistant. Indeed, surgical resection was historically the only therapy with demonstrated, albeit short-term, efficacy in true GISTs. However, even complete surgical resection of primary GIST carried a substantial risk for recurrence, i.e., surgery alone rarely resulted in a cure. **"Charles D. B., 2006"**

Although surgical resection is the standard of care for primary GISTs, roughly one half of patients with localized GISTs relapse after adequate surgery. For metastatic GISTs imatinib mesylate, a small molecule tyrosine kinase inhibitor active against BCR-ABL, KIT and PDGFR, is the standard of care. **"John R. Z., et al., 2005"**

Overall survival (OS) at 5 years for patients with GISTs has been reported to be 19% to 56% from various series. Complete resection has a major effect on survival. This was true even when achieving a complete resection involving the resection of multiple adjacent organs. Tumor grade was the second major factor that had an effect on survival and recurrence close. Follow-up with abdominal and pelvic computed tomography scanning beyond the usual 5- year is essential. **"Dematteo, et al., 2000"**