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Review of 45 gastrointestinal stromal tumors treated in a Brazilian hospital

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2024, 41(6):755–760

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OBJECTIVE **Review of clinicopathological features, diagnostic tools, complications, management, and outcomes of 45 gastrointestinal stromal tumors (GISTs) treated in 43 Brazilian patients.** METHOD **Analysis of records from a single hospital between 2015 and 2020 about management by video laparoscopy, and clinical, adjuvant, or neoadjuvant therapy; prognostic factors after resection including size, stage, mitotic count, free margin, complications, and the recurrence of the tumors.** RESULTS **Twenty-nine patients were women and the global mean age was 62.42±12.27 years. The sites of GISTs were: stomach (69.0%), jejunum and ileum (17.8%), and extra-gastrointestinal (13.2%). Tumor sizes were: <2 cm (24.4%), 2.0–3.8 cm (31.0%), 4.0–5.2 cm (9.0%), 7.0–9.5 cm (15.6%), 10.0–17.0 cm (13.3%), and 25.0–35.0 cm (6.7%), with fusiform (93.0%) and mixed (7.0%) cellularity. Video laparoscopic surgery treated 40% of cases, and four were for recidivism; adjuvant (57.8%) and neoadjuvant (2.2%) chemotherapies were utilized. The postoperative course was unremarkable in 20.0%, and infections occurred in 6.6% of the cases.** CONCLUSIONS **As a whole, the findings of the present review of cases are in accordance with the literature.**

Ανασκόπηση 45 στρωματικών όγκων του γαστρεντερικού που αντιμετωπίστηκαν σε νοσοκομείο της Βραζιλίας

Περίληψη στο τέλος του άρθρου

Key words

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Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors with origin in Cajal interstitial cells, affecting 10–20 people per million inhabitants per year, often presenting spindle cell morphology and immunohistochemistry positivity for CD117 (KIT) and DOG1, or CD34 if KIT is negative; and surgery is the effective treatment.[1–20] Mutations in KIT (75–90%) and in PDGFRA (10–20%) are found in GISTs.[1–7,10,12–14,17–20] They are usually (approximately 80%) found in patients over 50 years old; but people younger than 20 years with Carney's triad, Carney-Stratakis syndrome, and the type 1 neurofibromatosis can be affected (approximately 0.4%).[5,12] The main sites are the stomach (approximately 60%), small bowel (approximately 35%), large bowel (5%), and esophagus (1%), and are treated by surgery, adjuvant and neoadjuvant therapy.[1–20] Manifestations are non-specific, including anorexia, dyspepsia, nausea, abdominal pain, and gastrointestinal bleeding.[1,4,5,7,8,10,13,17–20] R0 surgery (complete resection of a localized tumor) without rupture of the tumor is the gold standard of management; however, as this hazardous complication is related to the tumor size, neoadjuvant therapy with a tyrosine kinase inhibitor (TKI) is used to reduce the risk of this event during the surgical manipulations.[2–4] Imatinib is the TKI which has been more commonly employed in the first-line management of the advanced and metastatic GISTs, and sunitinib, regorafenib, or avapritinib have been also utilized.[1–4,6–13,15–20] More recent treatment options are sorafenib, pazopanib, nilotinib, carbozantinib, rigorafenib, dovitinib, masitinib, ponatinib, lenvatinib, or immunotherapy with nivolumab and ipilimunab.[2,12,19] Procedures to treat gastric tumors by the stomach opening increase the risk of surgical infection.[17,19]

The aim of this retrospective study was to describe clinicopathological data of the GISTs treated in one hospital between 2015 and 2020, including the main features and respective outcomes.

MATERIAL AND METHOD

The present review involved 45 cases of GISTs affecting 43 patients who had surgery and chemotherapy in a Brazilian hospital of São Paulo-SP, with focus on age, gender, tumor site and size, manifestations, surgical and medical treatments, and postoperative follow-ups. The sizes were evaluated by the maximum tumor measure; surgical margins were classified as R0 resection (complete resection of a localized tumor), R1 resection (microscopic residual tumor), and R2 resection (grossly residual tumor); recurrence (appearance of macroscopic tumor at the site of resection); metastasis (appearance of tumor at distant sites of the resection); and tumor stage. Utilization of adjuvant or neoadjuvant chemotherapy was also included. Histopathological data (fig. 1) were evaluated by hematoxylin and eosin (H&E) staining. Cell types were categorized as spindled (>75% of the tumor), epithelioid (>75% of the tumor), or mixed (both types at least 25% of the tumor); nuclear atypia; mitotic activity; aspects of nucleoli and cytoplasm; hemorrhage and necrosis; lymphatic and blood vessels invasions, and lymph node implants. Mitotic index in most cellular tumor sections was counted as 5 mm^2 by a ×40 objective and ×10 ocular. The immunohistochemical analysis (fig. 2) utilized CD117, CD34, SMA, S-100, Desmin, and DOG1.

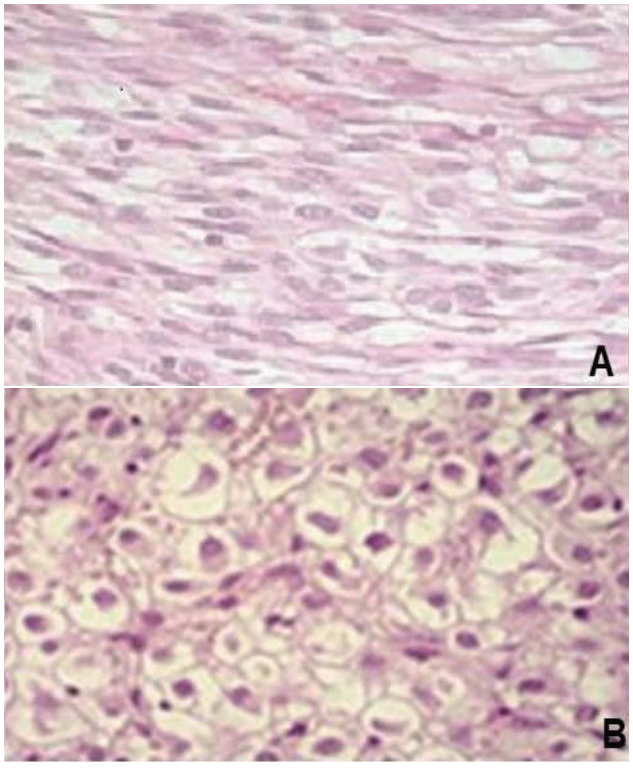

Figure 1. Histopathological fusiform and epithelioid patterns of gastrointestinal stromal tumors (GISTs) (H&E 400×) revealing spindle cells in intertwined bundles with vacuoles and ovoid nuclei with granular chromatin (**A**), and round epithelioid cells with abundant vacuolar cytoplasm and irregular nuclei with granular chromatin (**B**).

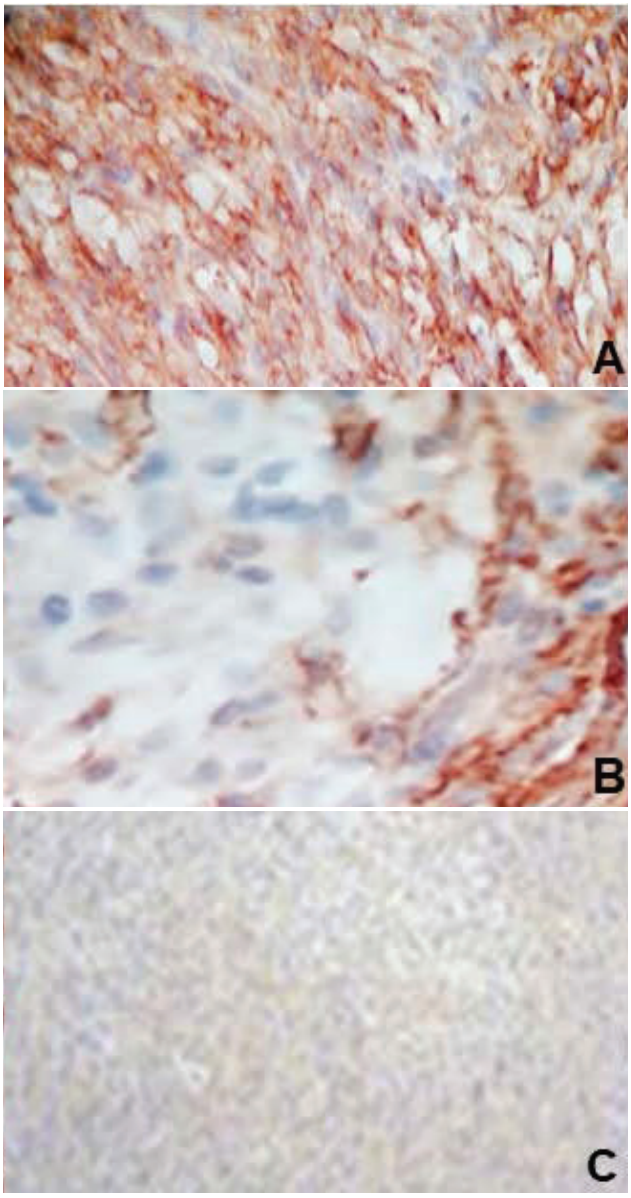

Figure 2. Immunohistochemistry study of neoplastic samples showing strong positivity for CD117 (200×) in **(A)** and for CD 34 (400×) in **(B),** and a weak diffuse staining for DOG-1 (100×) in **(C)**.

RESULTS

It is noteworthy that none of the patients included in this review informed a family antecedent of GIST. The tumors affected 29 (64.4%) females and 16 (35.6%) males distributed by the following age ranges: 43–49 (9/20.0%), 50–59 (10/22.0%), 60–69 (13/29.0%), 70–79 (8/18.0%), and 81–87 (5/11.0%) years. The mean age of the patients was 62.42±12.27 years, and females were 1.8 times more affected. The sites of these GISTs by order of frequency were the stomach (31/69.0%), jejunum and ileum (8/17.8%); extra-gastrointestinal and peritoneal (5/11.0%), and the

adrenal glands (1/2.2%). The tumors were categorized by their sizes into the following groups: <2 cm (11/24.4%), 2.0–3.8 cm (14/31.0%), 4.0–5.2 cm (4/9.0%), 7.0–9.5 cm (7/15.6%), 10.0–17.0 cm (6/13.3%), and 25.0–35.0 cm (3/6.7%); mitotic indexes were ≤5 mitosis/5 mm^2 (30/66.7%), and 5 mitosis/5 mm^2 (15/33.3%). The tumor stages were I (20.0%), IA (13.3%), IB (11.1%), II (24.4%), IIIB (17.7%), and IV (13.3%). Histopathological patterns of the tumors were fusiform (42/93.0%) and mixed (3/7.0%) cellularity. Video laparoscopic (VL) procedures were options to treat 18 (40.0%) of the cases, and 4 of them were by recidivism (one with 3.8 cm, and three measuring between 5.0 and 16 cm). These recurrent tumors were distributed into the stages I, IB, IIIB, and IV. The distribution of the 45 tumors by major diameters (in cm) was: 33% (0.5–2.0), 28% (>2.0–4.0), 11% (>4.0–6.0), 17% (>6.0–8.0), and 11% (>8.0). Imatinib (400 mg/daily or 800 mg/daily) adjuvant (26/57.8%) and neoadjuvant (1/2.2%) therapy were also utilized. Nine patients (20.0%) had unremarkable postoperative course, while nausea, vomiting, pain, and paralytic ileus occurred in 28 (62.2%), seroma and intra-abdominal collections in 4 (9.0%), infections in the operatory site in 3 (6.6%), and a cardiac disturbance in one patient (2.2%). There was no fatality during the early and late postoperative follow-up of this group of 43 patients.

DISCUSSION

The present review of records was performed in a single Brazilian hospital between 2015 and 2020 and included 29 female and 14 male patients, aged between 43 and 87 years, without family history; patients had GISTs (mainly gastric and of the small bowel), treated by surgery and chemotherapy. The tumor diameters varied from 0.4 to 25 cm; over two-thirds of the cellularity was fusiform, approximately 45% were tumors in stages I and II, and two-thirds of mitotic indexes were ≤5 mitosis/5 mm^2. The postoperative courses were unremarkable and there was no fatality outcome. Comparative findings of reviews from different populations with GISTs are also included.[2,9,11,17,20]

A systematic review of 42 studies, including the phases II and III, evaluated the efficacy of neoadjuvant and adjuvant, besides long-standing management of GISTs. The authors concluded that imatinib 400 mg daily is the first option for advanced or metastatic GISTs except for cases with mutation in PDGFRA exon 18 D842V or mutations in c-KIT exon 9; but 800 mg daily could be utilized before changing to second-line treatment with sunitinib or avapritinib, while regorafenib or ripretinib are used as a third- or fourth-line treatment in advanced or metastatic GISTs.[2]

The clinical characteristics and prognostic analysis of 45 high-risk GISTs affecting 27 females and 18 males with a mean age of 48 (28–77) years were described, and they had site in the stomach (42.2%), small intestine (20.0%), rectum (15.6%), retroperitoneum (13.3%), and mesentery (8.9%). All tumors were surgically treated by complete resection (77.8%) or resection of ruptured tumor (22.2%); 73.3% were R0, 11.1% R1, and 15.6% R2 resections, besides targeted therapy with imatinib. Recurrences occurred in 37.8% of cases, while survival rates were 100% in one year, 86.7% in three years, and 74.4% in five years. The authors concluded that the R0 resections played a major role to the improvement of the outcomes among patients presenting primary removable high-risk GISTs.[9]

A meta-analysis was performed to evaluate the prognostic impact of microscopically positive margins (R1) on primary GISTs up to November 2020; the disease-free survival (DFS) and the overall survival (OS) between R1 and R0 margins were estimated by a random-effects model. Twenty studies including 6,465 patients were analyzed and R1 was associated with a poor DFS in patients without adjuvant imatinib, but this negative impact disappeared with the adjuvant imatinib. Patients with R1 resection for rectal GIST had poor DFS even when they received adjuvant imatinib.

A retrospective study including the data of 1,019 patients with gastric GISTs from 13 Korean and 2 Japanese hospitals compared the postoperative and oncologic outcome of laparoscopic resection (n=318) for gastric GIST with open surgery (n=318). The laparoscopic group had fewer wound complications (0.6% versus 3.1%) and shorter hospitalization days (6.68±4.99 versus 8.79±6.50). The recurrence-free survival was similar, regardless of tumor sizes and sites, and risk classifications; tumors larger than 5 cm, high mitotic count, R1 resection, and rupture were risk factors for recurrence.

A review performed in 104 papers including health-related quality of life (HRQoL) outcomes and side effects of TKI therapy in GIST patients found that those treated with imatinib, regorafenib, and ripretinib had stable HRQoL, while those sunitinib-treated had decreased HRQoL. Almost all patients using TKIs had at least one adverse event, mild to moderate, not affecting HRQoL. The authors stressed the impact of side effects on the patient's daily live, dose reduction or interruption, and schedule adjustments to preserve the HRQoL, which can result in a longer duration of therapy.

In conclusion, the findings of the present review were in agreement with the literature on GISTs. Approximately 70% of tumors were localized in the stomach of female

Table 1. Data of 45 GISTs (gastrointestinal and other sites) treated in 43 patients during the period between 2015 and 2020.

No	Age	M/F	Fam	Site	Size (cm)	VL	Cells	Gr	Mitosis	Rup	Stage	Comp	*Rec	Adj	Neo
1.	43	F	N	G	8.0	N	Fus	I	≤5/5 mm³	N	IA	N	N	Y	N
2.	43	F	N	JI	3.6	N	Fus	I	≤5/5 mm³	N	IB	Y	Y	Y	N
3.	44	F	N	AG	9.5	N	Fus	I	>5/5 mm³	N	II	Y	N	Y	N
4.	44	M	N	G	2.8	Y	Mix	II	≤5/5 mm³	N	II	Y	N	Y	N
5.	46	M	N	G	0.5	S	Fus	I	≤5/5 mm³	N	I	Y	N	N	N
6.	47	F	N	JI	3.0	N	Fus	I	≤5/5 mm³	N	IA	N	N	N	N
7.	47	M	N	G	16.0	Y	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	N
8.	47	M	N	JI	3.8	N	Fus	I	≤5/5 mm³	N	I	N	Y	Y	N
9.	49	F	N	G	7.0	N	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	N
10.	50	F	N	G	1.7	Y	Fus	I	≤5/5 mm³	N	IA	Y	N	N	N
11.	51	M	N	JI	1.4	N	Fus	I	≤5/5 mm³	N	IB	Y	N	N	N
12.	53	F	N	G	1.5	N	Fus	I	≤5/5 mm³	N	I	Y	N	N	N
13.	55	F	N	G	7.5	Y	Fus	I	≤5/5 mm³	N	IB	Y	N	N	N
14.	55	M	N	G	10.5	N	Mix	I	≤5/5 mm³	N	II	Y	N	Y	N
15.	56	F	N	G	11.0	N	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	N
16.	57	M	N	G	1.5	Y	Fus	I	≤5/5 mm³	N	II	Y	N	Y	N
17.	58	F	N	G	3.1	Y	Fus	I	≤5/5 mm³	N	IA	Y	N	N	N
18.	59*	F	N	EGT	01/02/00	N	Fus	I	≤5/5 mm³	N	I	N	N	N	N
19.	59*	F	N	G	5.0	N	Fus	II	>5/5 mm³	N	IV	Y	N	Y	N
20.	60	F	N	G	7.0	Y	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	N
21.	61	M	N	G	1.4	N	Fus	I	≤5/5 mm³	N	IB	Y	N	N	N
22.	62	M	N	G	1.3	Y	Fus	I	≤5/5 mm³	N	I	Y	N	N	N
23.	63	F	N	G	9.0	N	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	Y
24.	64	F	N	G	3.0	Y	Fus	I	≤5/5 mm³	N	IA	N	N	N	N
25.	65	F	N	G	25.0	N	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	N
26.	65	F	N	EGT	1.3	N	Fus	I	≤5/5 mm³	N	I	N	N	N	N
27.	66	M	N	G	16.0	N	Fus	I	>5/5 mm³	N	IV	Y	N	Y	N
28.	66	M	N	G	17.0	Y	Fus	II	≤5/5 mm³	N	IV	Y	N	Y	N
29.	67*	F	N	JI	16.0	N	Fus	II	>5/5 mm³	N	IIIB	Y	Y	N	N
30.	67*	F	N	JI	4.0	N	Fus	II	>5/5 mm³	N	IIIB	Y	N	Y	N
31.	69	M	N	G	3.0	N	Fus	II	>5/5 mm³	N	IV	Y	N	Y	N
32.	69	M	N	G	3.1	Y	Fus	I	≤5/5 mm³	N	IA	Y	N	N	N
33.	70	F	N	G	2.0	Y	Fus	I	≤5/5 mm³	N	II	Y	N	Y	N
34.	70	M	N	EGT	0.4	N	Fus	I	≤5/5 mm³	N	I	N	N	Y	N
35.	70	M	N	G	1.5	N	Fus	I	≤5/5 mm³	N	II	Y	N	N	N
36.	71	F	N	EGT	2.0	N	Fus	I	≤5/5 mm³	N	I	N	N	N	N
37.	71	F	N	G	2.3	Y	Mix	II	>5/5 mm³	N	II	Y	N	Y	N
38.	72	F	N	JI	5.2	Y	Fus	I	≤5/5 mm³	N	IV	Y	Y	Y	N
39.	73	M	N	JI	2.3	N	Fus	I	≤5/5 mm³	N	II	N	N	Y	N
40.	79	M	N	G	4.5	Y	Fus	II	>5/5 mm³	N	II	Y	N	Y	N
41.	81	F	N	G	7.5	Y	Fus	I	≤5/5 mm³	N	I	Y	N	N	N
42.	84	F	N	G	28.5	N	Fus	I	≤5/5 mm³	N	II	Y	N	Y	N
43.	85	F	N	G	2.8	N	Fus	I	≤5/5 mm³	N	II	Y	N	N	N
44.	87	F	N	G	0.9	Y	Fus	I	≤5/5 mm³	N	I	Y	N	N	N
45.	87	F	N	EGT	35.0	N	Fus	II	>5/5 mm³	N	IV	Y	N	Y	N

F: Female, M: Male; Fam: Family antecedent; Y: Yes; N: No; G: Gastric, JI: Jejunum/ileum; AG: Adrenal gland; EGT: Extra gastrointestinal tract; GIST: Gastrointestinal stromal tumor; VL: Videolaparoscopy; Gr: Tumor grade; Rup: Rupture; Comp: Complication; *Rec: Recurrence; Adj: Adjuvant therapy; Neo: Neoadjuvant therapy

patients aged 40–70 years. Most of the 45 GISTs presented <2.0–3.8 cm sizes, spindle cell type, low-risk category, low tumor stage, mitotic count ≤5/5mm^2; only four recurrences, and none tumor rupture. The patients had successful laparoscopic surgery (40.0%), adjuvant (57.8%), and neoadjuvant (2.2%) chemotherapy. Early diagnosis and prompt resections are mainstays to better outcomes of primary removable GISTs.

ΠΕΡΙΛΗΨΗ

Ανασκόπηση 45 στρωματικών όγκων του γαστρεντερικού που αντιμετωπίστηκαν σε νοσοκομείο της Βραζιλίας

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ΣΚΟΠΟΣ Η ανασκόπηση των κλινικοπαθολογοανατομικών χαρακτηριστικών, των διαγνωστικών εργαλείων, των επιπλοκών, της διαχείρισης και των αποτελεσμάτων 45 στρωματικών όγκων του γαστρεντερικού σε 43 Βραζιλιάνους ασθενείς που αντιμετωπίστηκαν θεραπευτικά. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Ανάλυση αρχείων από ένα μόνο νοσοκομείο κατά το χρονικό διάστημα 2015–2020 σχετικά με τη διαχείριση μέσω λαπαροσκόπησης με video και την κλινική, επικουρική ή νεοεπικουρική θεραπεία, τους προγνωστικούς παράγοντες μετά την εκτομή, περιλαμβανομένου του μεγέθους, του σταδίου, του αριθμού των μιτωτικών διαιρέσεων, των επιπλοκών και της υποτροπής των όγκων. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Είκοσι εννέα ασθενείς ήταν γυναίκες με μέση ηλικία τα 62,42±12,27 έτη. Οι όγκοι εντοπίζονταν στον στόμαχο (69%), στη νήστιδα και στον ειλεό (17,8%), καθώς και στον εξωγαστρεντερικό σωλήνα (13,2%). Τα μεγέθη του όγκου ήταν: <2 cm (24,4%), 2–3,8 cm (31%), 4–5,2 cm (9%), 7–9,5 cm (15,6%), 10–17 cm (13,3%) και 25–35 cm (6,7%), με ατρακτοειδή (93%) και μικτή (7%) κυτταρική εμφάνιση. Με τη λαπαροσκοπική χειρουργική μέσω video αντιμετωπίστηκε το 40% των περιπτώσεων, ενώ 4 αφορούσαν σε υποτροπή. Χρησιμοποιήθηκαν επικουρικές (57,8%) και νεοεπικουρικές (2,2%) χημειοθεραπείες. Η μετεγχειρητική πορεία ήταν ομαλή στο 20%, ενώ λοιμώξεις εμφανίστηκαν σε ποσοστό 6,6% των περιπτώσεων. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Στο σύνολό τους, τα ευρήματα της παρούσας ανασκόπησης των περιπτώσεων ήταν σύμφωνα με τη βιβλιογραφία.

Λέξεις ευρετηρίου: Ανοσοϊστοχημεία, Διάγνωση, Διαχείριση, Στρωματικός όγκος του γαστρεντερικού

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