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ORIGINAL RESEARCH

Gastrointestinal Stromal Tumors Risk of Recurrence Stratification by Tumor Volume is a Best Predictor Compared with Risk Based on Mitosis and Tumor Size

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Abstract

Purpose Gastrointestinal stromal tumors (GIST) have the potential to recur and metastasize. Several prognostic schemes have been developed, mostly based on the mitotic count, diameter, and tumor site. However, these systems are not precise enough. The research question was whether the tumor size determined by volumetry allows a better risk stratification than the traditional system, and our aim was to determine the value of tumor volumetry, a feasible and simple parameter, in the recurrence of GIST.

Methods Seventy-four cases of GIST were studied. The cases presented with non-metastatic disease, which were resected and did not receive imatinib. We compared the clinico-pathologic features of the cases with recurrence against those with non-recurrence and compared the tumor volumetry against the classification system based on tumor size and mitosis.

Results The median age was 58 years (range: 25 to 91 years). Half of the cases were presented in the stomach. The tumor size had a median of 8 cm (range of 1–30 cm). The median mitosis count for 50 HPF was 4 (range 0–92). During the period of study, 16 (21.6%) patients suffered recurrence. The significant differences were that patients with recurrence accounted for more deaths and the follow-up period was larger. The area under the curve (AUC) of the volumetry classification was superior to the AUC of the classification system based on tumor size and mitosis (NIH-criteria) ($p = .05$).

Conclusion Tumor volumetry calculated in the surgical specimen and/or pre-operative tomography was superior to the NIH consensus in stratifying the risk of recurrence in GIST.

Keywords Gastrointestinal stromal tumors · GIST · Cancer · Recurrence · Volumetry

Introduction

GISTs, at one time, were thought to be quite rare, but because of an increased ability to reliably diagnose them, their incidence is now estimated at around 5000 new cases per year in the USA, which place them among the most common sarcomas [1].

It is considered that most GISTs have the potential to recur and grow in a diffuse way even after their complete excision and to acquire the ability of distant metastasis. In 2002, the National Cancer Institute (NIH) established a consensus for evaluation of their recurrence risk [2]. This scheme includes the anatomical site where the tumor is presented, the major diameter of the tumor and the number of mitosis in 50 high-power fields (50 HPF); however, a modification of this scheme obviated the location of the tumor. Nevertheless, there are cases in which one or more of these data are unknown, making it impossible to predict their risk of progression. It is therefore necessary to find different prognostic factors or a risk stratification system to apply them, by example, to cases where 50 HPF cannot be counted. Moreover, pre-operative assessment of GIST malignancy is not easy, and hence a more practical approach would be valuable.

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The recent development of imaging studies and the simplicity of determining tumor size by volumetry could be useful and practical for evaluating patients with GISTs, because the size in the risk assessment of GISTs refers to the single largest dimension, but GISTs are usually (almost every case) irregular tumors, and using a single dimension is an oversimplification of the more complex tumor. We hypothesize that a risk stratification system based only on tumor volumetry (measured with computer tomography and/or in the surgical specimen) could predict the risk of recurrence in patients with GIST, better than the NIH consensus criteria based on size and mitotic count. The research question was whether the tumor size determined by volumetry allows a better risk stratification than the traditional system, and our aim was to compare the diagnostic performance for recurrence of NIH consensus criteria against risk stratification based on tumor volume in uninodular, previously untreated primary GISTs.

Material and Methods

This work was approved by the Research Ethics Committee of the National Cancer Institute of Mexico (approval number: Rev/70/17). Surgical specimens of primary (non-metastatic) uninodular GISTs without prior treatment were selected from the pathological files of our Institution between 1995 and 2015 relating to patients older than 18 years, who had at least 1 year of clinical follow-up, with no prior treatment (including imatinib) ($n = 74$). Clinical and histological characteristics were recorded from the patients' clinical files.

The patients were classified into four risk groups, following the NIH consensus criteria (Table 1) based on the tumor size in largest dimension and mitotic count in 50 HPF. With the three largest diameters of the tumors measured in the surgical specimens and in the pre-surgical tomography (taking the diameters settled in the radiology report), tumor volume was calculated with the formula of the volume of an ellipsoid ($(4/3) \times \pi \times r1 \times r2 \times r3$). Then, a ROC curve was created to identify cut-off points of tumor volume determined in the surgical specimen associated with recurrence. Based on the ROC results, tumors were grouped into three categories, both for the surgical specimen (0–250 cm^3, 251–1200 cm^3, and > 1200 cm^3) and for the pre-surgical tomography image (0–200 cm^3, 201–1150 cm^3, and > 1150 cm^3).

Basal features of the patients with recurrence were compared with those of patients without recurrence during follow-up. For the comparison of numerical variables and based on a normality test (Kolmogorov-Smirnov test), a Mann-Whitney U test was performed. For the comparison of qualitative variables, a chi-square or Fisher exact test was used, according to the frequency of observed events. Likewise, area under the curve (AUC) was calculated and a comparison by the chi-squared test was performed between the AUC of the NIH consensus risk stratification and the AUC of the classification based on volumetry. For all the statistical tests, a value of $p \leq .05$ was established as the significance level. All statistical procedures were performed in STATA ver. 14.1 (StataCorp, Texas, USA) and were reviewed by a statistician.

Results

Basal Characteristics of the Patients

Of the 74 cases of GIST analyzed, 37 (50%) cases occurred in women. The median age was 58 (age range: 25 to 91 years). Half of the cases presented in the stomach. The tumor size had a median of 8 cm (range of 1–30 cm). Regarding the pathological characteristics, 60.5% cases were spindle cell, 30.2% were mixed, and 9.3% were epithelioid. A total of 11.6% cases showed skenoid fibers, 27.9% had intra-tumoral lymphoid aggregates, 4.7%

Table 1 National Institute of Health (NIH) Consensus Criteria for recurrence risk stratification of Gastrointestinal Stromal Tumors

Risk category	Tumor size in largest dimension	Mitotic count in 50 high power fields
Very low risk	< 2 cm	< 5
Low risk	2–5 cm	< 5
Intermediate risk	< 5 cm	6–10
	5–10 cm	<5
High risk	> 5 cm	> 5 mitosis
	> 10 cm	Any mitotic count
	Any size	> 10 cm

Modified from: Fletcher CD et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002; 33; 459–465

Table 2 Clinico-pathological characteristics of 74 patients with gastrointestinal stromal tumor (GIST) according to recurrence of the disease

Variables	GIST non-recurrent *n = 58*	GIST recurrent *n = 16*	*p-value**
Sex—no. (%)			
Female	30 (51.7)	7 (43.8)	.572
Male	28 (48.3)	9 (56.2)	
Outcome—no. (%)			
Alive free of disease	49 (84.5)	9 (56.3)	*.015*
Dead of disease	9 (15.5)	7 (43.8)	
Tumor site—no. (%)			
Stomach	31 (53.4)	6 (37.5)	.259
Non-stomach	27 (46.6)	10 (62.5)	
Prognostic group (risk of recurrence) —no. (%)			
Very low risk	4 (6.9)	0	.647
Low risk group	10 (17.2)	2 (12.5)	
Intermediate risk group	15 (25.9)	4 (25)	
High-risk group	29 (50)	10 (62.5)	
Volume group in specimen—no. (%)			
< 250 cm3	38 (65.5)	6 (37.5)	.107
250–1200 cm3	14 (24.1)	6 (37.5)	
≥ 1200 cm3	6 (10.3)	4 (25)	
Volume group in specimen—no. (%)			
< 200 cm3	38 (65.5)	6 (37.5)	.321
201–1150 cm3	15 (25.8)	7 (43.8)	
≥ 1150 cm3	5 (8.7)	3 (18.7)	
Age—median (IQR)	58 (45–65)	59 (49–68)	.537
Tumor size in cm—median (IQR)	8 (5–13)	11 (6–19)	.198
Mitosis / 50 fields—median (IQR)	4 (0–6)	5 (1–15)	.501
Tumor volume in cm3—median (IQR)	112.9 (32.9–515.3)	470 .6 (46.6–1334.5)	.198
Follow-up in months—median (IQR)	26 (11–40)	46 (35–60)	*.003*

* For categorical variables chi-square test. For numerical variables Mann-Whitney *U* test

Italic entries are probabilities

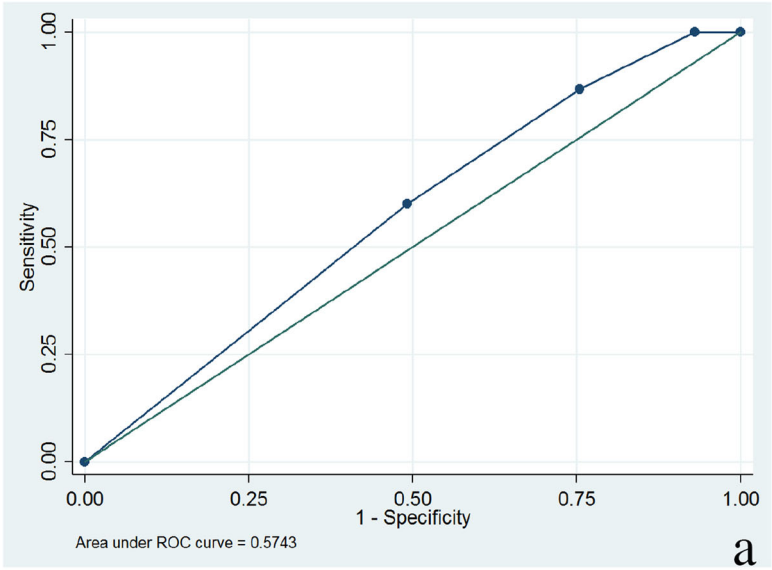
n Number of patients

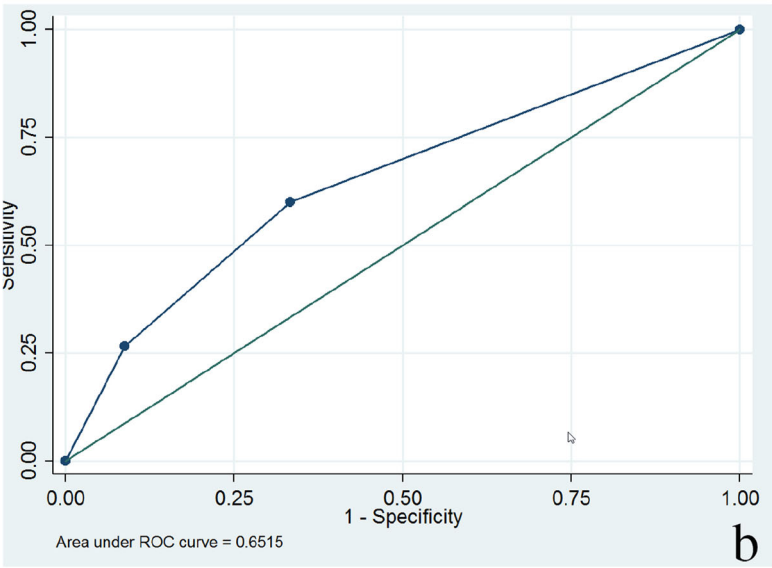
cases had rhabdoid cells, 27.9% presented invasion to the mucosa with ulceration, and 23.3% presented marked pleomorphism. The median mitosis count for 50 HPF was 4 (range 0–92).

Table 3 Comparison of classifications for risk of recurrence in GIST

Classification	Sensibility (%)	Specificity (%)	Correctly classified (%)	+ LR	− LR	AUC	98% C.I.	*p*
NIH consensus								
Very low risk	100	0	20.83	1.0	0	.574	.43–.715	Ref.
Low risk	100	7	26.39	1.07	0			
Intermediate risk	86.67	24.56	37.5	1.14	0.54			
High risk	60	50.88	52.78	1.22	0.78			
Volumetry (specimen)								
< 250 cm^3	100	0	20.83	1.0	0	.651	.5–.803	.05
250–1200 cm^3	60	66.67	65.28	1.8	0.6			
≥ 1200 cm^3	26.67	91.23	77.78	3.0	0.8			
Volumetry (tomography)								
< 200 cm^3	100	0	20.8	1.0	0	.618	.493–.732	.07*
201–1150 cm^3	80	29.8	40.28	1.14	0.6			
≥ 1150 cm^3	60	64.9	63.89	1.71	0.6			

NIH National institute of Health, *GIST* gastrointestinal stromal tumors, *LR* likelihood ratio, *AUC* area under the curve, *C.I.* confidence interval





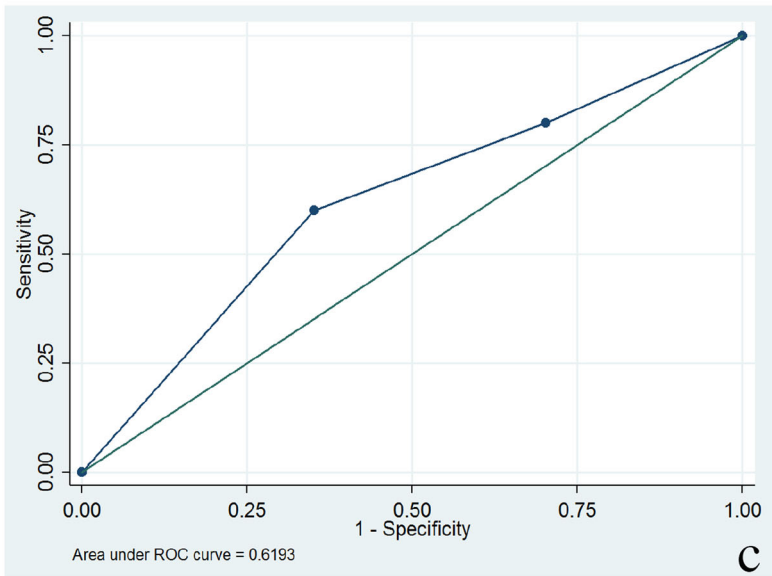


Fig. 1 Area under the curve (AUC) comparison between three classifications of the risk of recurrence grouping of GIST. **a** AUC of the National Cancer Institute consensus system of classification of GIST in four groups (AUC = 0.5743). **b** AUC of the classification in three categories using tumor volumetry in the surgical specimen in patients without adjuvant or neoadjuvant therapy (AUC = 0.6515). **c** AUC of the classification in three categories using tumor volumetry in the pre-surgical tomography in patients without adjuvant or neoadjuvant therapy (AUC = 0.6193)

The patients had a median follow-up of 31 months (range 12–131 months) and during this period, disease recurred in 16 (21.6%). At the end of the study period, the 16 patients died.

Comparison of Groups with and Without Recurrence

We compared the clinical and pathological characteristics of patients with recurrent GIST ($n = 16$) with patients with non-recurrent GIST ($n = 58$), results of which are summarized in Table 2. The significant differences were that death of patients with recurrence was more and the follow-up period was longer. None of the other characteristics assessed was significantly different between the groups.

Comparison of Risk of Recurrence Classification Systems

The NIH risk of recurrence classification was compared with volumetry-based groups, with respect to the ability to discriminate the presence of recurrence. The results are described in Table 3. As Table 3 and Fig. 1 show, the AUC of the classification was superior to the NIH consensus, with statistical significance ($p = .05$). In a stratified analysis, the AUC of the volumetry in cases located at the stomach was 0.732, compared to 0.519 from the NIH classification ($p = .037$). For cases arising in other sites than the stomach, the AUC for the volumetry was 0.613 compared to 0.532 form the NIH classification ($p = .047$).

Discussion

In the present study, we show that volumetry could be a tool for stratifying in groups the recurrence risk of patients with GIST, independently of the site and without histopathology parameters. The stratification is based on volumetry, both in the surgical specimen and in tomography, and was superior to the NIH consensus classification in our series.

This has not been reported before, but some information about the usefulness of volumetry on GIST is available. Trumani et al. [3] previously reported that estimation of tumor volume in primary GIST using the mathematical formulae of ellipsoid volume is feasible, because GISTs are rarely spherical (and in cases where they are indeed spherical, we can use the sphere formula for volume calculation) and the segmented volumes were highly concordant with three axis-based scalene ellipsoid volumes. They found that this method is feasible, reproducible, and even comparable to the automated method (based on the Carestream Vue PACS Lesions Management Software, Carestream Health, Inc. N.Y.). In another report, Hashiba et al. [4] followed the growth of a small GIST and calculating their doubling time (which was 3.3 months); they deducted a high growth rate and malignancy. Thereafter, they performed a gastric resection and found that the GIST had 15–16 mitoses per 50 HPF, indicating malignancy. The patient was found to have hepatic metastasis 27 months after the surgery, confirming the malignant behavior of the tumor. Finally, volumetry has also been used to evaluate tumor response to medical treatment [5].

The most important risk factors for conventional GISTs are the anatomic site, size, and mitotic rate [6]. Other important risk factors are tumor rupture and mucosal invasion; however, true mucosal invasion is rare and subjective, so it is not now incorporated into the major risk stratification schemes for GIST [7]. Based on these parameters, several risk stratification schemes have been proposed. The first scheme that was established, the NIH Consensus Criteria: used mitotic rate and size to determine the risk of recurrence (Table 1) [2]. After it was established, its utility was confirmed in series with long-term follow-up [8, 9]. Based on several large studies, the Armed Forces Institute of Pathology (AFIP) modified the NIH Consensus criteria to add anatomic sites including the stomach, duodenum, jejunum/ileum, and rectum [10], and these criteria are recommended by the College of American Pathologists (CAP) [11]. Joensuu has proposed a simplification to the AFIP criteria that groups anatomic sites into either gastric or non-gastric sites, to show that gastric tumors have a better prognosis. Further, he subdivided mitotic rate into three categories instead of two: less than or equal to 5, 6–10 and greater than 10 mitotic figures per 50 HPF. Finally, he added tumor rupture as automatic criteria for determining a GIST as high risk.

Less complex classifications are needed because the major use of risk stratification criteria is for determining who should and should not receive adjuvant therapy after resection, and the ability to definitively find a few high-risk categories is helpful. Also, pre-surgical estimation of the risk of recurrence is valuable. We presented a simple and feasible classification in three categories, involving all tumor locations; however, we find some limitations. First, the follow-up time of the group of patients with no recurrence in our series was shorter than those with recurrence. Second, since the diameter evaluation was not performed in a systematic fashion by an expert radiologist, we have taken the diameter as settled in the radiology reports; however, this reflects the diary practice, where we have only the radiological report. Third, our series is small and our data needs to be validated in a larger series.

Conclusions

We found tumor volumetry by applying a mathematical formula, a simple, promising, and feasible method to classify into groups with risk of recurrence of primary GISTs, surgically treated and without administration of adjuvant therapy. This method was superior to the NIH consensus in predicting

recurrence; however, due to the very selected and small sample size of our study, our results need to be validated.

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Declaration of authorship All authors meet the criteria for authorship as per the guidelines of the International Committee of Medical Journal Editors (ICMJE), and all have participated at (1) conception or design of the work or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version submitted; and (4) agreement to be accountable for all aspects of the work regarding the accuracy or integrity of the research.

Compliance with Ethical Standards

This study was conducted following the statements of Helsinki declaration and was approved by the Ethics in Investigation Board of our Institution with a waiver of informed consent.

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Patil DT, Rubin BP. Gastrointestinal stromal tumor: advances in diagnosis and management. Arch Pathol Lab Med. 2001;135(10): 1298–310.
2. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33: 459–65.
3. Tirumani SH, Shinagare AB, O'Neill AC, Nishino M, Rosenthal MH, Ramaiya NH. Accuracy and feasibility of estimated tumour volumetry in primary gastric gastrointestinal stromal tumours: validation using semiautomated technique in 127 patients. Eur Radiol. 2016;26(1):286–95.
4. Hashiba T, Oda K, Koda K, Takiguchi N, Seike K, Miyazaki M. A gastrointestinal stromal tumor in the stomach: usefulness of computed tomographic volumetry. Gastric Cancer. 2004;7(4):260–5.
5. Schramm N, Englhart E, Schlemmer M, Hittinger M, Übleis C, Becker CR, et al. Tumor response and clinical outcome in metastatic gastrointestinal stromal tumors under sunitinib therapy: comparison of RECIST, Choi and volumetric criteria. Eur J Radiol. 2013;82(6):951–8.
6. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39(10):1411–9.
7. Rutkowski P, Bylina E, Wozniak A, Nowecki ZI, Osuch C, Matlok M, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour—the impact of tumour rupture on patient outcomes. Eur J Surg Oncol. 2011;37(10):890–6.
8. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005;117(2):289–93.
9. Martin J, Poveda A, Llombart-Bosch A, et al. Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol. 2005;23(25):6190–8.
10. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2): 70–83.
11. Rubin BP, Blanke CD, Demetri GD, Dematteo RP, Fletcher CD, Goldblum JR, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor. Arch Pathol Lab Med. 2010;134(2):165–70.