Mucosal Ulceration in Gastrointestinal Stromal Tumor is an Independent Predictor of Progression-Free Survival

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Introduction

- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the GI tract [1,2]
- Known prognostic features of GISTs include tumor mitotic rate, size, location, and mutation [3,4]
- The prognostic significance of mucosal ulceration in GISTs remains unknown

Aim: further characterize the significance of ulcerated GISTs and its impact on patient prognosis

Hypothesis: tumor ulceration is an independent prognostic factor of GISTs

Methods

Retrospective study of patients with a suspected diagnosis of primary GIST between the years of 2000 and 2020

513 patient medical records in the UCHealth system were identified using Health Data Compass Data Warehouse and data were recorded using REDCap; 310 patients met criteria

- Include if: 18y/o + with documented GIST diagnosis
- Exclude if: Inadequate records, metastatic at initial dx

Primary outcome:

- Ulceration, confirmed by definitive documentation in the endoscopic or histopathologic report
- Tumor progression, defined as local or metastatic recurrence of GIST

Secondary outcomes:

- Known and potential associated clinicopathologic prognostic factors

Disclosures and References

The authors have no relevant disclosures to share. This study was deemed exempt from IRB review (#20-1678) by the Colorado Multiple Institution Review Board (COMIRB) at the University of Colorado Anschutz Medical Campus, and by the Protocol Review Monitoring System at the University of Colorado Cancer Center.

1. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer. 2005 Feb 15;103(4):821-9. doi: 10.1002/cncr.20862. PMID: 15648083.
2. Goetsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. Eur J Cancer. 2005 Dec;41(18):2868-72. doi: 10.1016/j.ejca.2005.09.009. Epub 2005 Nov 15. PMID: 16293410.
3. Demattteo RP, Gold JS, Saran L, Gönen M, Liau KH, Maki RG, Singer S, Besmer P, Brennan MF, Antonescu CR. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer. 2008 Feb 1;112(3):608-15. doi: 10.1002/cncr.23199. PMID: 18076015.
4. Jiang Z, Zhang J, Li Z, Liu Y, Wang D, Han G. A meta-analysis of prognostic value of KIT mutation status in gastrointestinal stromal tumors. Onco Targets Ther. 2016 Jun 3;9:3387-98. doi: 10.2147/OTT.S101858. PMID: 27350754; PMCID: PMC4902249.

Table 1: Indication leading to GIST diagnosis

Indication	Total (n=310) N (%)	Ulceration (n=85) N (%)	No ulceration (n=225) N (%)	P-value*
IDA	**43 (13.9)**	**24 (28.2)**	**19 (8.4)**	**<.0001**
GIB	**87 (28.1)**	**56 (65.9)**	**31 (13.8)**	**<.0001**
Dyspepsia / dysphagia	9 (2.9)	1 (1.2)	8 (3.6)	.45
Abdominal Pain	112 (36.1)	29 (34.1)	83 (36.9)	.65
Incidental finding	**104 (33.6)**	**5 (5.9)**	**99 (44.0)**	**<.0001**

*P values are either chi-square or Fisher's exact.

Table 2: Factors significantly associated with ulceration

Characteristic	Ulcerated Group (n=85) N (%)	Non-ulcerated Group (n=225) N (%)	P-value
Tumor diameter (cm)			
≤5.0	**32 (37.7)**	**138 (61.3)**	**<.001**
5.1 - 10	**35 (41.2)**	**49 (21.8)**	
>10	**18 (21.2)**	**38 (16.9)**	
Mitotic index			
≤5/50 HPF	**53 (62.3)**	**186 (82.7)**	**<.001**
>5/50 HPF	**32 (37.7)**	**39 (17.3)**	
Specific Exon Mutation			
KIT Exon 11	**34 (40.0)**	**56 (24.9)**	**.009**
GI bleeding			
Yes	**58 (68.2)**	**37 (16.4)**	**<.0001**
No	**27 (31.8)**	**188 (83.6)**	
Risk classification*			
Very low / low	**33 (42.9)**	**132 (64.7)**	**<.0001**
Intermediate	**5 (6.5)**	**23 (11.3)**	
High	**39 (50.7)**	**49 (24.0)**	
Tumor progression			
Yes	**34 (40.0)**	**32 (14.2)**	**<.0001**
No	**51 (60.0)**	**193 (85.8)**	

Table 3: Multivariable regression, significant independent risk factors for disease progression

Parameter		Hazards ratio [95% CI]	Cox Regression P-value (95%)
Tumor Diameter	**≤5.0**		**.003**
	5.1 - 10	2.1 [0.92 – 5.0]	
	>10	**5.0 [2.0 – 12]**	
Mitotic Index	**≤5/50 HPF**		**<.001**
	>5/50 HPF	**3.1 [1.6 – 6.0]**	
Specific Exon Mutation	**KIT Exon 9**	**3.6 [1.2 -11]**	**.02**
Ulceration	**Yes**	**2.4 [1.2 – 4.7]**	**.01**
	No		

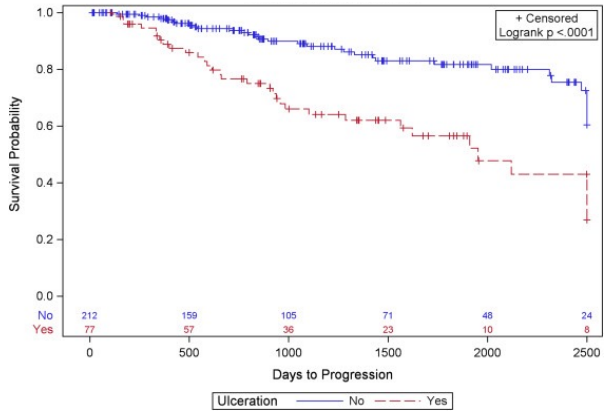

Figure 1. Progression-free survival by Kaplan-Meier analysis of patients with and without ulcerated GIST

Results

- 27.4% of patients had an ulcerated tumor.
- GI bleeding and iron deficiency anemia were significantly more likely to be presenting symptoms for GIST in patients with ulceration (Table 1).
- After a median follow-up of 35.4 (IQR=17.1-62.2) months, ulceration was significantly associated with tumor diameter (p<.001), mitotic index (p<.001), gastrointestinal bleeding (p<.0001) and stated risk classification on pathology reports (p<.0001) (Table 2).
- KIT Exon 11 mutations were significantly associated with ulcerated GISTs (40.0% vs 24.9%, p=.009) (Table 2).
- 40.0% of patients with ulcerated tumors had a progression event compared to only 14.2% of patients with non-ulcerated tumors (p<.0001) (Table 2).
- After correcting for covariates ulceration remained a significant independent risk factor for tumor recurrence or progression (HR=2.4, [1.2 – 4.7], p=.01) (Table 3).
- Kaplan-Meier analysis also confirmed inferior PFS estimates with ulcerated GIST (Figure 1, p<.0001).

Discussion

Ulceration is a significant independent risk factor for the progression of gastrointestinal stromal tumors

- Results confirm the known prognostic significance of tumor size, mitotic index, and KIT Exon 9
- First known study to investigate the prognostic significance of ulcerated GISTs, and the largest known study to focus specifically on evaluation of ulceration as a primary outcome
- Ulceration may be a risk factor that could influence risk-based treatment decisions in patients with GIST
- Limitations: retrospective; lack standardized reporting
- Further prospective evaluation of ulcerated GIST prognostic significance is warranted

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