Research article

Epidemiology, prognostication and treatment outcome of gastrointestinal stromal tumour: A single centre prospective study

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ABSTRACT

Introduction and Aim: GI stromal tumours (GISTs) being most frequent mesenchymal tumours of the alimentary tract have few studies on epidemiology in this subcontinent. The current prospective study is aimed at gathering data on the molecular epidemiology and possible effect of molecular markers on standard pathological prognostic factors and also to measure the overall disease outcome.

Materials and Methods: In this prospective epidemiologic study conducted from 2016 to 2019, all GIST patients registering at the Radiotherapy Department of IPGME & R, Kolkata, India; identified by histopathology were prescribed pre-specified immune-histochemical tests and offered a protocolized treatment. The patients were followed up for a minimum of twelve months and on average for thirty months, to watch for disease progression.

Results: A total of 38 patients with median age 49.5 years with male predominance (p= 0.005) presented most commonly with abdominal pain (42.1%); jejunum (31.6%) followed by stomach (26.3%) being most common sites, spindle cell type (78.9%) being commonest histological type. Immunohistochemistry showed positive expression for SMA (7.9%), DOG1 (28.9%), CD34 (31.6%), CD117/cKIT (65.8%). CD117 positivity (Rho= -0.366, p=0.024) has negative association with mitotic count, whereas DOG1 (Rho=.513, p=0.001) and CD34 (Rho=.459, p=0.004) positivity have positive association with tumour dimension. DOG1 positivity was found to be a contributing factor of disease progression (RR 12.57, p=0.035).

Conclusion: In sub-continental patients, gender and age distribution of GISTs differ from western countries but not pathological features. Molecular markers have important prognostic significance.

Keywords: GIST; CD117; DOG1; progression free survival.

INTRODUCTION

Gastrointestinal stromal tumours (GIST) is the most common mesenchymal neoplasm of the alimentary tract (1). The most common site of involvement of GIST is the stomach followed by the small intestine and rarely extraintestinal as in the omentum, retroperitoneal region and other organs (1).

Histologically, GISTs are typed into Mixed types (10%); Epitheloid (20%) Spindle-cell (70%; 1-3). The current immuno-histologic perspective of diagnosing GISTs evolved after development of several other molecular manifestations apart from CD117/KIT mutations (1,2). CD117, a product of cKIT, a type III receptor tyrosine kinase that binds with stem cell factor followed by dimerization and phosphorylation is described as to involve in Ras-Erk, Arc and PI3K/AKT pathway helping in cell proliferation and growth progression (3). The presence of gain-of-function mutations, controversially, in some other types of tumour such as angiosarcoma or melanoma has raised the requirement of battery of differentiating tests, such as CD34, SMA and Vimentin as to find lineage of smooth muscle cells. CD34 and SMA were found to be more consistent apart from CD117 in differentiating GISTs (4). Discovery of DOG1 transcripts independent of KIT/PDGFRA and its highly specific association with GIST has helped in the molecular diagnosis of it (5), though DOG1 positive extra intestinal leiomyomas should be classified separately. Carney triad syndrome may include gastric GISTs as its component (6). In 2002 the first National Institute of Health risk based classification of GIST was proposed after an elaborated consensus document by Fletcher *et al.,* (7) came into light. Tumour size and mitotic rate are main factors of risk stratification. Benign tumours are of size of <2.0 cm with low mitotic activity [less than 5 mitoses per 50 high-power fields], whereas tumours exhibiting more than 5 mitoses per 50 HPFs are considered to be malignant and bear higher probability of recurrence and disease progression (8). In 2006 evaluating1,765 gastric and 906 small-intestinal GISTs. Miettinen and colleagues proposed a new Armed Forces Institute of Pathology (AFIP) classification of GIST where anatomical location had emerged as a new prognostic factor (9). Later on Joensuu and associates included tumour rupture

during surgery as a poor prognostic factor in the modified NIH classification (10). However, though immunohistochemical subtypes have been evident in diagnosis of GIST, there is no clear consensus about their role in prognosis or risk stratification, in spite of many authors proposing their significant contribution in disease progression, recurrence and survival (11). Treatment of GIST is primarily surgery followed by targeted therapy(12).

The Indian Council of Medical Research (ICMR) guidelines have directed that the evaluation of a suspected patient should be done with standard white light endoscopy and multiple biopsies along with multidetector computed tomography of abdomen pelvis and optionally of thorax besides blood investigations (13).

This study is aimed to gather the data on the clinical and pathological aspect and to review the prognostic effect of molecular markers. There are only a few studies on GIST based on the Indian population and no rigorous data from the eastern part of India.

MATERIALS AND METHODS

We performed a prospective study by including all the patients coming in the department of Radiotherapy, of our Institute with a tissue diagnosis of GIST. The recruitment started in the month of July 2016 and data of all patients up to January 2019 are included with a minimum 12 months of follow up of the last recruited patient. Total 38 patients were reported with GIST, and the immunohistochemical profile was performed using a panel of CD117, CD34, DOG1, vimentin and SMA. Risk stratification was done using AFIP risk stratification system.

IBM® SPSS 20.0 software was used for statistical analysis. Prognostic correlation is done using Pearson correlation coefficient. The Kaplan-Meier method is used to assess progression-free survival. The prognostic model was formulated using binary logistic regression analysis.

RESULTS

Demographics and symptomology

The demographic symptomatologic characteristics of the patients is summarized in Table 1.

Pathology and histopathology

Primary location of the disease was observed to be highest in jejunum (31.6%) and stomach (26.3%). Next most common site was duodenum (15.8%). Colon (5.3%), Rectum (2.6%) and anal canal (2,6%) harbored a minority of the disease. Among extraintestinal GIST peritoneum (7.9%) was the commonest site followed by retroperitonium 5.3%). Histologically spindle cell type (80%) outnumbered the other types such as epitheloid and mixed type with a statistically significant margin. 44.7% of the patients presented with a T2 disease, showing significantly commonest tumor stage of presentation. Mean tumor dimension was 6.5 cm, ranging from 1.5 cm to 15 cm. Very few patients presented with a node positive (5.3%) or metastatic (15.8%) disease mainly at the liver. Mitotic count, an important prognostic component of pathological features, was measured in 34 of the patients showing median 5 mitoses per 50 high power fields. Summary of the pathological characters are delineated in Table 2.

Table 1: Demographic characters

Characteristics	**Patients with GIST** (n=38)	**Proportional Significance**
Age of the patients		
Mean *Range*	49.5 Y (95% CI= 45-51 Y) 32-72 Y	
Sex		
Female *Male*	10 (26.3%) 28 (73.7%)	p= 0.005
Symptom Present *Pain abdomen* *Back pain* *Malena* *Lower GI bleed* *Non-specific* *Other pain* *symptoms*	 16 (42.1%) 4 (10.5%) 8 (21.1%) 5 (13.2%) 3 (7.9%) 2 (5.3%)	
Symptom duration before presentation Median	6m (1-92 months, SD=24)	

Table 2: Pathologic characteristics

Characteristics	**Patients with GIST** (n=38)	**Proportional Significance**
Site of Presentation		
Stomach *Duodenum* *Jejunum* *Colon* *Rectum* *Anal Canal* *Peritoneal* *Retroperitoneal*	10 (26.3%) 6(15.8%) 12(31.6%) 2(5.3%) 1(2.6%) 2(5.3%) 3(7.9%) 2(5.3%)	P=0.001 (p= 0.87 between stomach and jejunum)
Histology		
Spindle Cell Type *Epitheloid* *Mixed*	30 (78.9%) 7 (18.4%) 1 (2.6%)	p= <0.001
T stage		
T0 *T1* *T2* *T3* *T4*	1 (1%) 3 (7.9%) 17 (44.7%) 9 (23.7%) 9 (23.7%)	P=0.015
N Stage		
N0 *N1*	36 (94.7%) 2 (5.3%)	p= <0.001
M Stage		
M0 *M1* Liver Metastasis Peritoneal Metastasis	32 (84.2%) 6 (15.8%) 5 (13.2%) 1 (2.6%)	p= <0.001
Tumour dimension (maximum)	Mean- 6.54 cm 95% CI- 5.14 - .93cm	-
Mitotic Count	Median-5/50HPF 95% CI-4-7/50 HPF	-
Risk Categories High Intermediate Low Very low	 13 14 11 0	

Table 3: Molecular characteristics

Characteristics (Positivity)	**Patients with GIST** (n=38)	**Proportional Significance**
CD 117/ cKIT	25 (65.8)	0.003
DOG1	11 (28.9)	0.03
CD34	12 (31.6)	0.02
SMA	3 (7.9)	-
Vimentin	2 (5.3)	-
Prognostic correlation		
Maximum dimension *DOG1* *CD34*	 R= 0.513 p=0.001 R=0.459 p=0.004	
Mitotic count *CD117*	R=(-)0.366 p=0.024	

65.8% of the patients reported CD117/cKIT positivity which is proportionally very high. CD 34 being the next most common marker came to be positive in 31.6% of cases followed by DOG1(28.9%). SMA and Vimentin also showed insignificant presence. The correlation study of the molecular markers and classical pathological prognostic markers were done. Presence of CD117 had negative correlation with

mitotic count (p=0.024), probably indicating its positive prognostic value. On the other hand, greater tumor dimension has positive correlation with the presence of DOG1 (p=0.001) and CD 34 (p=0.004). (Table 3)

Treatment and its outcome

Almost all and 76% of the patients were offered surgery and Imatinib mesylate in standard dose (400 mg orally once a day) respectively. All CD117 positive patients were among them. Hazard of toxicity was low, with 13% absolute toxicity event and mean time to produce toxicity being 7.6 months. In thirty months of follow up period absolute disease progression rate was 13% only, with mean PFS being 26.6 months. Mean time to produce disease progression is 14 months (95% CI= 4.6-23 months; Table 4).

Table 4: Treatment and outcome[1]

Surgery	
None	1 (2.6)
Resection	6 (15.8)
Gastrectomy and Splenectomy	1 (2.6)
Total Gastrectomy	1 (2.6)
Subtotal Gastrectomy	1 (2.6)
Wedge Resection	4 (10.5)
APR	1 (2.6)
Colostomy	1 (2.6)
Inoperable	3 (7.9)
Chemotherapy	
Imatinib	29 (76.3)
Toxicity of chemotherapy	
Events	5 (13.2)
Mean time to produce toxicity	7.6 months (95% CI= 4.2-11 months)
Progression after treatment	
Events	5 (13.2)
Mean time for disease progression	14 months (95% CI= 4.6-23 months)
30 months Progression free survival	26.6 months (95% CI= 23-30 months)

[1]values indicate frequency, values in parentheses indicate % unless mentioned otherwise

The progression event has been tested for logistic regression on pathological and important molecular prognostic variables. The classical prognostic factors e.g., tumour dimension and mitotic count per 50 HPF did not show significant contribution in the logistic model. Among the molecular markers, DOG1 mutation showed significant contribution to disease progression (Relative Risk= 12.57, p=0.035; Table 5).

Table 5: Logistic regression model of prognostication (Dependant variable= Progression event)

Risk element	RR	Significance
Maximum Dimension	1.01	p= 0.967
Mitotic Count	1.13	p= 0.584
CD117 negativity	1.4	p= 0.734
DOG1 positivity	12.57	**p= 0.035**
CD34 negativity	1.3	p= 0.772

RR= Relative risk

DISCUSSION

The global epidemiologic data has been systematically reviewed by Søreide *et al.*, reflecting information of 13550 patients from 29 studies (14). The pooled data showed the mean age of incidence is in the mid-sixties. Gastric location was found to be more frequent, accounting to more than fifty percent of patients followed by small bowel (31.8%). Oesophagus is stated as the rarest gastrointestinal site of harbouring the tumour. The current study has shown the mean age of incidence is at a somewhat younger age-group as in the late fifth decade of life. This is supported by most of the Indian studies, where late forties or early fifties were the mean age of incidence, reflecting an assumption of earlier age of incidence of GIST in the South Asian population. Another aspect of difference between western studies and subcontinental data is the sex ratio. Soreide *et al.*, (14) reported almost equal incidence of GIST among male and female population, whereas, in line with the current study the male preponderance of GIST is evident in literature published from the Indian population. Pain (15) and GI bleed (16) are the most common symptoms as described in the Indian literature, as does the current study. There is a very high incidence of cKIT/CD117 positivity found in most of the studies. Although only very recent studies have included DOG1 as a molecular marker, it is seen to be very much associated with GIST.

Vershney *et al.*,(17) did an univariate and multivariate analysis on hazard function for recurrence free survival on many demographic, clinical and pathologic factors. On univariate analysis size, mitotic activity, nuclear pleomorphism are seen to have a

significant predictive role on recurrence, but nuclear pleomorphism was the single significant contributor in multivariate analysis. Cyriac *et al.,* did univariate analysis on progression free survival where presence of liver metastasis, anemia and CKIT exon 11 mutation were found to be statistically significant affecters (18). The current study, however, emphasised on pathological factors including molecular markers as the driver of prognosis. Effect of molecular markers on progression free survival has not been discussed in detail in most Indian studies. In a multinomial logistic model the current study showed greater tumour dimension, higher mitotic count, CD117/cKIT negativity, CD34 negativity and DOG1 positivity have shown to be the contributors of the disease progression but DOG1 was found to be only statistically significant among them. On the other hand correlation exists between components of Fletcher criteria of risk stratification and molecular markers. CD117 has been shown as an indicator of better prognosis as it has an inverse relationship with mitotic count. On the other hand DOG1 and CD34 have direct relationship with tumour dimension and probably on tumour growth. In the logistic model the involvement of DOG1 in disease progression and relapse may be related to its molecular mechanism of action on cell growth. Though the DOG1 has long been discussed as a diagnostic marker in GIST, especially in KIT-negative tumours, its prognostic impact was debatable. The study by Rizzo *et al.,* concluded that DOG1 expression does not only overlap with cKIT expression in 66% of the patients, but it has been linked with worse two year relapse free survival, indicating its possibility of being a factor of poor prognosis (19). Şahin *et al.,* proposed that due to high specificity of DOG1 and its role in determining prognosis, it should be routinely included in the immunohistochemical analysis of a suspected GIST (20). The current study also shows outstanding prognostic contribution of DOG1 positivity on GIST, with evidence of which this paper strongly supports its inclusion in prognostic stratification.

Limitation of the current study is the small sample number and intermediate duration of follow up. Practically a long term follow up report of GIST is lacking worldwide. Besides due to rarity of the disease a large number of patients could not be included in this single institutional study.

CONCLUSION

In sub-continental Asian patients, gender and age distribution of GISTs differ from western countries but not the pathological features. With complete treatment, there is a low rate of progression of disease and survival probability has been increased. Molecular markers may have important prognostic significance.

CONFLICT OF INTEREST

The authors express no conflicts of interest.

REFERENCES

1. Miettinen, M., Lasota, J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23:70-83.
2. Patel, N., Benipal, B. Incidence of gastrointestinal stromal tumors in the United States from 2001-2015: a United States Cancer Statistics analysis of 50 states. Cureus. 2019 Feb; 11(2): e4120.
3. Babaei, M. A., Kamalidehghan, B., Saleem, M., Huri, H.Z., Ahmadipour, F. Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. Drug Des Devel Ther. 2016;10:2443-2449.
4. Hirota, S., Isozaki, K., Moriyama, Y., Hashimoto, K., Nishida, T., Ishiguro, S., Kawano, K., Hanada, M., Kurata, A., Takeda, M., Muhammad Tunio, G., Matsuzawa, Y., Kanakura, Y., Shinomura, Y., Kitamura, Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279:577-580.
5. Espinosa, I., Lee, C. H., Kim, M. K. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Pathol. 2008; 32:210-218.
6. Zhang, L., Smyrk, T. C., Young Jr, W. F., Stratakis, C. A., Carney, J. A. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviourally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. Am J Surg Pathol. 2010; 34(1):53-64.
7. Fletcher, C. D., Berman, J. J., Corless, C., Gorstein, F., Lasota, J., Longley, B. J., *et al.,* Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459-465.
8. Agaimy, A. Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting. Int J Clin Exp Pathol. 2010;3(5):461-471.
9. Miettinen, M., Lasota, J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130:1466-1478.
10. Joensuu, H., Martin-Broto, J., Nishida, T. Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery. Eur J Cancer. 2015;51:1611-1617.
11. Schmieder, M., Henne-Bruns, D., Mayer, B., Knippschild, U., Rolke, C., Schwab, M., *et al.,* Comparison of different risk classification systems in 558 patients with gastrointestinal stromal tumors after R0-Resection. Front Pharmacol. 2016;7:504-506.
12. Panizo-Santos, A., Sola, I., Vega, F., de Alava, E., Lozano, M. D., Idoate, M. A. Predicting metastatic risk of gastrointestinal stromal tumors: Role of cell proliferation and cell cycle regulatory proteins. Int J Surg Pathol. 2000;8:133-144.
13. Shrikhande, S. V., Sirohi, B., Barreto, S. G., Chacko, R. T., Parikh, P. M., Pautu, J., *et al.,* Indian Council of Medical Research consensus document for the management of gastrointestinal stromal tumors. Indian J Med Paediatr Oncol. 2014;35(4):244-248.
14. Søreide, K., Sandvik, O. M., Søreide, J. A., Giljaca, V., Jureckova, A., Bulusu, V. R. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer epidemiology. 2016;40:39-46.
15. Rajappa, S., Muppavarapu, K. M., Uppin, S., Digumarti, R. Gastrointestinal stromal tumors: a single institution experience of 50 cases. Indian J Gastroenterol. 2007;26(5):225-229.

16. Lakshmi, V. A., Chacko, R. T., Kurian, S. Gastrointestinal stromal tumors: A 7-year experience from a tertiary care hospital. Indian J Pathol Microbiol. 2010;53:628-633.
17. Varshney, V. K., Gupta, R. K., Saluja, S. S., Tyagi, I., Mishra, P. K., Batra, V. V. Analysis of clinicopathological and immunohistochemical parameters and correlation of outcomes in gastrointestinal stromal tumors. Indian J Cancer. 2019;56:135-143.
18. Cyriac, S., Rajendranath, R., Sagar, T. G. Gastrointestinal stromal tumor: Analysis of outcome and correlation with c-kit status in Indian population. Indian J Cancer. 2014;51:35-39.
19. Rizzo, F. M., Palmirotta, R., Marzullo, A., Resta, N., Cives, M., Tucci, M., *et al.,* Parallelism of DOG1 expression with recurrence risk in gastrointestinal stromal tumors bearing KIT or PDGFRA mutations. BMC Cancer. 2016;16:87-88
20. Şahin, S., Ekinci, Ö., Seçkin, S., Dursun, A. The diagnostic and prognostic utility of DOG1 expression on gastrointestinal stromal tumors. Turk Patoloji Derg. 2017;33(1):1-8.