A RETROSPECTIVE SINGLE CENTRE AUDIT ON GASTRIC GASTROINTESTINAL STROMAL TUMOURS OVER A PERIOD OF FIFTEEN YEARS

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DECLARATION

I, Suzanne Kuhn, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Dr Suzanne Kuhn

Signed on the tenth day of November 2021

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To my loving and supporting husband and children, for always understanding when I have to spend time at work in order to get the work done. An impossible task to complete alone.

LIST OF TABLES AND FIGURES

ABBREVIATIONS

GIST	Gastrointestinal Stromal Tumour
MDT	Multidisciplinary team
NIH	National Institute of Health
PDGFRA	Platelet derived growth factor alpha
HPF	High power field
PACS	Picture Archiving Compter System
ROC	Receiver Operating Characteristics

PUBLICATION READY MANUSCRIPT

Spindle cell subtype gastric GISTS dominate the proximal stomach. A Retrospective Audit on Gastric Gastrointestinal Stromal Tumours presenting to Groote Schuur Hospital

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Key words

Gastrointestinal stromal tumour, stomach, GIST

ABSTRACT

Introduction: Gastrointestinal stromal tumours (GIST) are the commonest tumour of mesenchymal origin; favour the stomach, and account for a very small percentage of gastrointestinal tract tumours.

Methods: In this retrospective audit of GISTs presenting to the Groote Schuur Hospital surgical and oncological multidisciplinary team (MDT) between 2004 – 2019, gastric GISTs were evaluated as regards presentation, gastric anatomical position, histological subtype with risk stratification, management and outcomes.

Results: Of 126 GIST tumours presenting to this MDT, 82 originated in the stomach. Complete histopathological records could be obtained for 64. With an average of 59 years (50 male: 32 female), 18 (28%) presented with a herald bleed. Other common presentations included anaemia, epigastric mass and pain. The tumours were predominantly found in the body and fundus (64%), with a spindle cell subtype predominance (41%). The association between cancer cell subtype and gastric position was not significantly different (p=0.728). Cystic degeneration was found on 11 (17%) analyzed and cell necrosis on 12 (18%). These findings were not related to larger tumor size or prognosis. Five required downstaging with Imatinib prior to surgery. Thirty-seven patients underwent a surgical procedure: 24 wedge resections and 12 anatomical resections. Risk stratification was performed with the modified National Institutes of Health (NIH/Fletcher) score. Twenty-eight cases had inaccurate mitotic counts and couldn't be scored, 17 scored high risk, 9 intermediate risk, 9 low risk and 1 very low risk. Ten patients died of metastatic disease, 34 were discharged with no disease progression after 3 years, 1 patient with disease progression currently remains on Imatinib, and 19 were lost to follow up.

Conclusion: Gastric GISTs appear to have a predilection for the proximal stomach; it is unsure whether this is purely due the greater surface area. The spindle cell subtype dominated in the proximal gastric GISTs. Cystic degeneration and cell necrosis did not seem to be related to larger tumours or outcomes.

INTRODUCTION

While gastrointestinal stromal tumors (GIST) are very low incidence tumours (10-15 per million), they are the commonest mesenchymal tumor of the gastrointestinal tract (GIT) originating from the interstitial cells of Cajal (1). Gastrointestinal stromal tumours may develop anywhere in the GIT but are most frequently seen in the stomach (55.6%) (1). The small bowel (25%) and colon and rectum (10%) follow as regards prevalence. (1) The majority of gastric GISTs occur sporadically in a fairly equal sex distribution, with only a small percentage (<5%) attributable to a syndromic background.(2) Mutations within the *KIT* proto-oncogene and platelet derived growth factor receptor alpha (*PDGFRA*) are now well established as the background events leading to the formation of most GISTs.(3, 4) The outcomes of locally advanced or metastatic GISTs have much improved since the establishment of imatinib, a tyrosine kinase inhibitor, as treatment in mutation sensitive tumours.(5-7) Variations including *KIT* exon 9, *PDGFRA* exon 18 and wildtype *KIT* and *PDGFRA* are either less sensitive or not responsive to imatinib and will require treatment dosage adjustments, second line tyrosinase inhibitors or pioneering molecular compounds such as avapritinib, ripretinib and cabozantinib.(2, 8, 9)

Surgical GIST management depends on the gastric region involved, tumor size, staging and risk stratification of the specific tumour. In early disease, segmental or wedge resection with 1 – 2cm clear margins has been the mainstay of treatment(10, 11). If necessary, neoadjuvant imatinib can successfully reduce tumour size and subsequently improve chances of resectability with gastric preservation.(12, 13) Imatinib reliably achieves disease control in 75-80% of patients with advanced disease by suppressing tumour progression in the long-term(14, 15).

The presence of spindle/epithelioid type cells confirms the diagnosis, with GISTs sub-classified into spindle cell (70%), epithelioid (20%) and mixed type (10%).(16) Suitable biopsies and surgical specimens can provide adequate mitotic indices per 50 high power field (Hpf), which will indicate potential for malignant activity and influence subsequent management(17). Mitotic count, tumor size and anatomical location within the GIT are added into the modified National Institutes of Health (NIH/Fletcher) (18), which serves as a predictor of tumour malignancy and objectively influences management strategies at multidisciplinary level.(19, 20)

Sporadic GISTs are not frequently described as regards their regional incidence and tumour characteristics within specific gastric anatomical locations, often simply being labelled as gastric GISTs. Mention has been made of the tendency of multiple sporadic GISTs of the stomach to appear to cluster in the proximal stomach; we aim to confirm our hypothesis that even single sporadic gastric GISTs have a preponderance towards the proximal stomach.(2) As such we describe tumour characteristics of gastric GISTs with a focus on their prevalence according to specific gastric anatomical regions. In addition, validating the NIH (Fletcher) risk scoring system in our patient sample and correlating outcome and metastatic disease with tumour position, subtype and size in a low-and middle-income country (LMIC) such as South Africa with economical restrictions as regards routine mutational analysis and availability of imatinib is key.

METHODOLOGY

Participants

This was a single center 15-year retrospective audit between 1 January 2004 and 30 December 2019. All patients with histologically confirmed gastric GISTs were extracted from an approved database for inclusion into this study. The study was performed at the University

of Cape Town according to the principles outlines by the Helsinski declaration. A total of 88 patients with gastric GISTs were identified for possible analysis. Only complete records were included, resulting in a total of 64 patients being eligible for analysis.

Patient demographics and clinical variables

Patient demographics and baseline clinical variables were obtained according to standard protocols. Staging CT scans were accessed via the local Picture Archiving and Communication System (PACS) system. Tumour size, gastric location and the presence of metastatic disease was recorded. If this information was unobtainable on the PACS system (installed locally in 2012, hard copies of cross-sectional imaging reports were retrieved from patient folders.

Confirmation of the immunohistochemistry results were obtained via the National Health Laboratory Service (NHLS) online access system. Cell subtype, mitotic count, cystic changes and cell necrosis were recorded. Tumour size was confirmed by the pathological reports of all surgically removed tumours where possible, or purely on cross-sectional imaging. Primary tumour site within the stomach was described according to a combination of cross-sectional imaging, position at endoscopy and, if performed, as noted at surgery. In addition, tumour stage, surgical intervention performed, the use of chemotherapeutic agents (neoadjuvant and adjuvant) and 3-year outcomes were recorded. The prevalence of gastric GISTs to specific gastric anatomical regions was evaluated in relationship to gastric area.

Gastric Area

A two-dimensional estimation of gastric area was determined by defining gastric anatomical regions on a normal barium meal. Only barium meals with a normal report as per the investigating radiologist within the last year of this study's timeframe were included for possible evaluation. A complete image of the entire stomach on a single anterior-posterior frame, with a clear insertion of the oesophagogastric junction plus incisura easily visible, was

essential for inclusion. The area of these defined anatomical regions was then calculated in centrimeters^2 using the programming available on the local Phillips IntelloSpace PACS Enterprise (version 4.4.553.50) system via the freehand region of interest function. This resulted in the possibility of a size comparison between the fundus, body and antrum in centimeters^2 for an individual stomach. (Appendix 1). As double contrast barium meals are infrequently performed nowadays at our institution, we accept that these calculations are not necessarily an accurate depiction of a fully expanded stomach, but rather serve as confirmation that the fundus is indeed the smallest area of the stomach.

Data management and analysis

Demographic variables and clinical data as detailed in the previous sections were previously recorded on a password-protected database as per institutional ethical guidelines. From this database we extracted relevant data for the purposes of this study that was similarly managed using a secure password protected electronic database. Statistical computations were made using IBM SPSS statistics (version 27.0, IBM, USA). Statistical significance was set as $p < 0.05$. Continuous data were reported as mean ± SD or mean ± SEM and discreet data as percentages. In addition to reportive statistics, we assessed Area Under the Curve (AUC) of Receiver Operating Characteristic (ROC) Curves to evaluate the performance of validated risk scores in the prediction of clinical outcomes and mortality. Curves were generated on SPSS as mentioned previously.

Ethics

Approval for this database was obtained by the University of Cape Town Surgical Departmental Research Committee and the University of Cape Town Human Research Ethics Committee (registry HREC 031/2015; sub-study HREC 859/2019 with a subsequent

amendment approved to increase the time frame of data collection to a 15-year period and include an estimation of gastric area as calculated on normal barium meal imaging).

RESULTS

Study Population

During the period January 2014 to December 2019, a total of 126 gastrointestinal stromal tumours were diagnosed at Groote Schuur Hospital. The majority were gastric GISTs (n=84, 65%) with 64 patients with complete patient records evaluated for the purposes of this study. The 44 non-gastric GISTs included oesophageal (n=1, 1%), small bowel (n=28, 22%), colorectal (n=7, 6%), peritoneal (n=4, 3%) and unknown primary origin (n=4, 3%).

Table 1. Descriptive characteristics of 64 patients with gastric gastrointestinal stromal tumours.

VARIABLE	MEAN (SD)/NUMBER (FREQUENCY)
Demographics	
Age mean (SD), years	59.5 (13.5)
Gender – male	32 (50 %)
Tumour characteristics	
*Tumour size**	
0-20 mm	1 (2 %)
21-50 mm	14 (22 %)
50-100 mm	10 (16 %)
> 100 mm	24 (38 %)
not measured**	15 (23 %)
Tumour position	
Cardia	6 (9 %)
Fundus	17 (27 %)
Body	24 (38 %)

Antrum	2 (3 %)
Pylorus	1 (2 %)
Multicentric	2 (2 %)
Large overlapping anatomical sites	12 (19 %)
Tumour subtype	
Spindle	26 (40 %)
Epithelioid cell	6 (9 %)
Mixed (spindle and epithelioid)	11 (17 %)
Not reported on	21 (33 %)

Continuous variables expressed as mean (± standard deviation), median (interquartile range) or proportions as appropriate.
mm: millimeter.
*Tumour size determined by computerized tomography scan imaging or by excised pathology specimen.
**Size not accurately documented; hard copies of imaging not available.

Patient and Tumour Characteristics

Demographic characteristics of the 64 patients with gastric GISTs can be seen in Table 1. At the time of presentation, the mean age was 59.5 (SD 13.5) years with both genders equally represented (50%). With regards to tumour size, 24 (38 %) of tumours measured more than 100 mm in size. Tumour distribution varied but was predominantly located in the fundus (n=17, 27 %) and body (n=24, 38 %) of the stomach. Spindle cell was the most predominant histological subtype (40%).

Surgical and Oncological Treatment

Within this group, 45 % (n=37) of patients were considered potentially resectable and 31 % (n=25) of patients were palliated with long term Imatinib. Surgical and oncological interventions offered for the resectable gastric GISTs can be seen in Table 2. A small minority required downstaging with preoperative Imatinib; while in most a primary wedge resection (65%) was the prevailing surgical procedure offered. Primary wedge resections showed favourable outcomes and 96 % (n=23) of patients had no disease progression 3 years after surgical intervention.

Histological Subtype

Figure 1 depicts tumour subtypes in relation to anatomical position within the stomach. Spindle cell subtype was the most prevalent in all areas. Histological reports described additional cellular changes. Cystic degeneration in 20% (n=13), tumor necrosis in 28% (n=18) and both in 6% (n=4) of cases. Cystic degeneration and tumour necrosis were absent in 52% (n=33) of cases.

Table 2. Surgical and oncological treatment of 37 patients with resectable GIS Ts

	CHEMOTHERAPY (n, percentage)				OUTCOME OVER 3 YEARS (n, percentage)	
	NEO-ADJUVANT	ADJUVANT	ADJUVANT AND NEO-ADJ	NO CHEMOTHERAPY	NO DISEASE PROGRESSION	DECEASED
Wedge resection,	0	3 (13 %)	3 (13 %)	18 (75 %)	23 (96 %)	1 (4 %)
Subtotal gastrectomy,	1 (33 %)	2 (66 %)	0	0	3 (100 %)	0
Total gastrectomy	0	2 (50 %)	0	2 (50 %)	3 (75 %)	1 (25 %)
Total gastrectomy and splenectomy	0	2 (66 %)	0	1 (33 %)	2 (66 %)	1 (33 %)
Gastrectomy, omentectomy and modified D2	0	1 (100 %)	0	0	1 (100 %)	0
Staging laparoscopy	0	0	1 (100 %)	0	0	1 (100 %)

Continuous variables expressed as mean (± standard deviation), median (interquartile range) or proportions as appropriate.

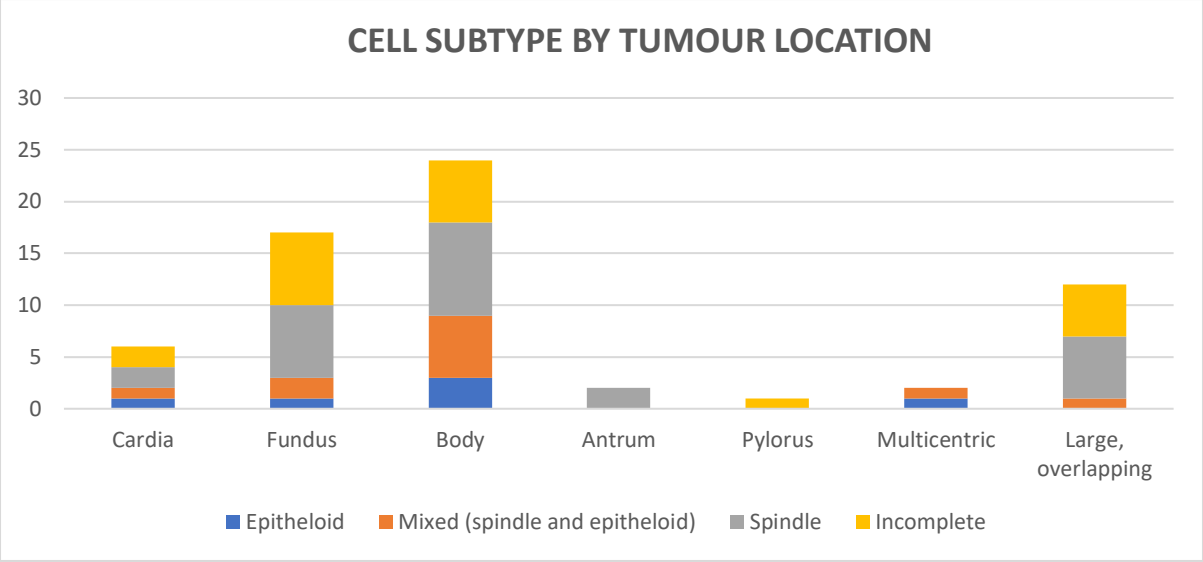


Figure 1. Histological subtype in relation to gastric location.

Multicentric: More than one tumour in various gastric sites; Large, overlapping: large tumour overlapping more than one area.

Prognostic indicators in relation to metastatic disease

Prognostic indicators used in the NIH (Fletcher) grading score, can be seen in Table 3. Of patients who presented with tumours larger than 100mm, 56% (n=13), had metastatic disease at presentation. Tumour size was not measured in 23% (n=15) of cases due to the unavailability of cross-sectional hard copies and absence of accurate documented tumour dimensions. Mitotic counts were measured at inaccurate magnification and deemed insufficient for measurement per 50 high power fields in 44% (n=28) of tumours. Subsequently NIH (Fletcher) scores could not be calculated in these cases. NIH (Fletcher) scores were documented as high risk in 34% (n=22) of cases and 27% (n=6) of these had metastatic disease at presentation.

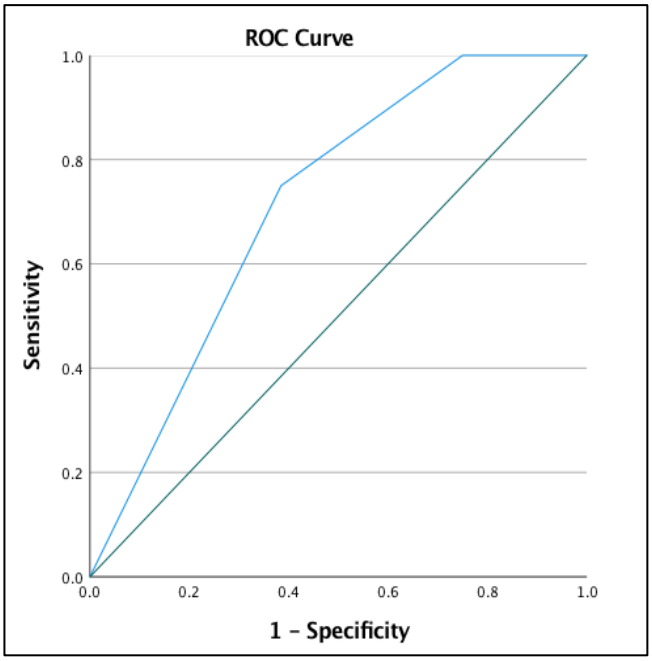
Table 3. Prognostic indicators in relation to metastatic disease.

	METASTASES (n=23)	NO METASTASES (n=41)
Tumour Size		
0-20 mm	0	1 (2.4 %)
21-50 mm	1 (4.3 %)	13 (31.7 %)
51-100 mm	1 (4.3 %)	9 (22.0 %)
> 100 mm	13 (56.5 %)	11 (26.8%)
Not determined*	8 (34 %)	7 (17.1 %)
Mitotic Count		
≤ 5 in 50 hpf	4 (17,4 %)	22 (53,7 %)
6 – 10 in 50 hpf	0	3 (7,3 %)
> 10 in 50 hpf	3 (13 %)	4 (9,8 %)
Insufficient sample for accurate mitotic count	16 (69,6 %)	12 (29,3 %)
NIH (Fletcher) Risk Score		
Very low	0	0
Low risk	1 (4.3 %)	5 (12.2 %)
Intermediate risk	0	7 (17.1 %)
High risk	6 (26.1 %)	16 (39 %)
Insufficient sample for accurate mitotic count	16 (69.6 %)	13 (31.7 %)
Anatomical tumor position		
Cardia	2 (8,7%)	4 (9,8%)
Fundus	8 (34,8%)	9 (22%)
Body	6 (26,1%)	18 (4,3%)
Antrum	0	2 (4,9%)
Pylorus	1 (4,3%)	0
Mulyicentric*	0	2 4,9%)
Large, overlapping sites*	6 (26,1%)	6 (14,6%)

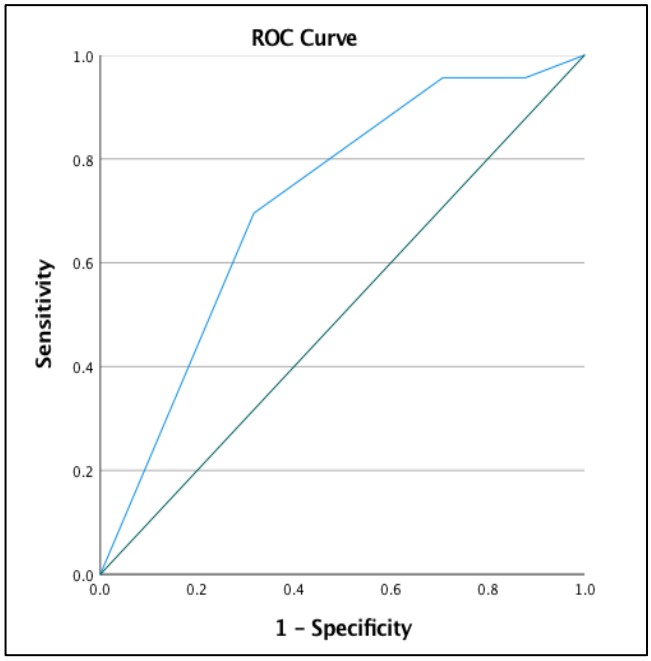
Data represented as number (proportion); mm: millimeters; hpf: high power fields; NIH: National Institute of Health. *Size not accurately documented Data; hard copies of imaging not available.
*Multicentric: More than one tumour in various sites; large, overlapping: Large tumour overlapping more than one area.

NIH (Fletcher) risk score

We assessed the performance of the NIH (Fletcher) risk score in the prediction of clinical outcomes including metastases and mortality, in figure 2. For both the confirmed presence of metastases and mortality, the NIH (Fletcher) risk score served as favorable predictor of these events (AUC 0.715, *p*=0.005 and AUC 0.714, *p*=0.022 respectively). A comparison of 3-year outcome in relation to NIH (Fletcher) grading score showed a favorable 3-year survival in all 4 risk groups 67% (n= 43), as depicted in table 4. The mitotic index measurement was taken at a lower high-power field in 43% due to inadequate tissue obtained at biopsy. These cases fell in the non-surgically managed group, ie. more advanced tumours that could not be excised. They could therefore not be classified accurately into the NIH (Fletcher) scoring system.



NIH (FLETCHER) RISK SCORE VS MORTALITY



NIH (FLETCHER RISK SCORE VS METASTASES

RECEIVER OPERATOR CHARACTERISTIC CURVE	AREA UNDER CURVE	p
NIH (Fletcher) risk score as a predictor of mortality	**0.714**	**0.022**
NIH (Fletcher) risk score as a predictor of metastatic disease	**0.715**	**0.005**

Figure 2. Fletcher risk score as a predictor of mortality and of metastases.

NIH (FLETCHER) RISK SCORE	SURVIVED	DECEASED	LOST TO FOLLOW UP
Very low	0	0	0
Low risk	6 (14 %)	0	0
Intermediate risk	6 (14 %)	0	1 (11,1 %)
High risk	17 (39,5 %)	3 (25 %)	2 (22,2 %)
Insufficient mitotic count	14 (32,6 %)	9 (75%)	6 (66,7 %)

Table 4. Three-year outcome in relation to NIH (Fletcher) grading score

Tumor prevalence and outcomes in relation to anatomical position

In order to demonstrate the significance of the tumour numbers to gastric anatomical region we firstly established the obviously smaller area of the proximal stomach (cardia and fundus) in relation to the gastric body and antrum. Two-dimensional anatomical surface area was apportioned on 20 normal barium meals. The anatomical regions were divided into proximal stomach (cardia and fundus), gastric body and distal stomach (antrum and pylorus).The average size of the proximal stomach was 29,6cm^2, the body 67,27cm^2 and the distal stomach 24,47cm^2. Relative to surface area, a higher incidence of tumours was confirmed within the smaller proximal stomach. The proximal fundus had a total of 27% (n=17) GIST tumors. Presence of metastatic disease in relation to tumour position is depicted in table 3. There

was also a higher incidence of metastatic disease at diagnosis in tumours positioned in the fundus 34,8 % (n= 8).

DISCUSSION

This study affirms that GISTs favour the stomach. In addition, we are able to report that gastric GISTs have a predilection for the proximal stomach, with a noticeably high incidence in the smaller fundal area. Fundal tumours were also associated with a higher incidence of metastatic disease. In addition to reporting on location, we report on histological findings with spindle cell as predominant gastric subtype. This is in keeping with previous literature (9). The present study also serves as validation of the NIH (Fletcher) risk score with significant implication for resource limited healthcare settings such as South Africa where accurate risk stratification is essential to allow for appropriate resource distribution.

Considering the smaller surface area, the high prevalence of tumours located in the fundus was unexpected. A proposed explanation for this could be the embryological origins of these tumors. GISTs originate from the Interstitial cells of Cajal, in the smooth muscle layer of the GIT.(21) These cells originate from neural crest cells. Morphologically different cells from ICC appear at the end of the embryological period. c-*KIT* positive cells appear firstly in the oesophagus and stomach, then in small bowel and lastly in large bowel. They emerge in a rostro-caudal gradient, in a similar way as the neural crest cells colonizes the digestive tube. (21, 22)There is a distinguishable difference in appearance of c-*KIT* positive cells in the stomach, esophagus and duodenum when compared to the rest of the small bowel. The small bowel cells form a very narrow chain, in the outer portion of the wall, immediately beneath the serosa. A proposed explanation for this is the presence of ventrally immigrating neural tube cells (VENT), populating the foregut in a much larger number of c-*KIT* positive cells.(21)

These VENT cells are only relevant in the foregut, giving rise to the oesophagus, stomach, and first part of the duodenum. (23) Could these cells dominate the smooth muscle lining in the more proximal regions of the stomach, therefore giving rise to a higher prevalence of GISTs in the fundus?

Spindle cell is the predominant gastric GIST subtype reported, confirmed again by our findings (9). Histological subtype is not frequently discussed as a prognostic factor. In addition, we found no significance between increased tumour size or more aggressive disease at presentation, to the presence of tumor necrosis or cystic degeneration on histological evaluation. In 52% of cases neither of these histological findings were present. The majority of aggressive metastatic fundal tumors were incompletely classified into subtypes, possibly due to the insufficiently sized biopsies taken when making the diagnosis for metastatic disease. We therefore cannot comment on relation of tumor subtype to the more aggressive fundal tumors. A meta-analysis by Yi *et al* concluded that the presence of tumor necrosis was associated with a decrease in disease free survival time, recurrence and overall survival.(24) The rate of tumor necrosis were noted to be higher in high risk groups in one study, but the finding was not statistically significant.(25) An interesting observation was that 73% of the cases with tumor necrosis present in our study were all of the spindle cell subtype. All tumors with necrosis documented on histological reports were larger than 50mm in size, which could support the theory of possible inadequate blood supply developing in larger tumours. If the tumor outgrows its blood supply due to rapid growth or tumour size, there will be subsequent tumor necrosis.

We validated the NIH (Fletcher) risk score according to disease severity and mortality. Disease severity was considered to be advanced if patients presented with metastatic disease. For

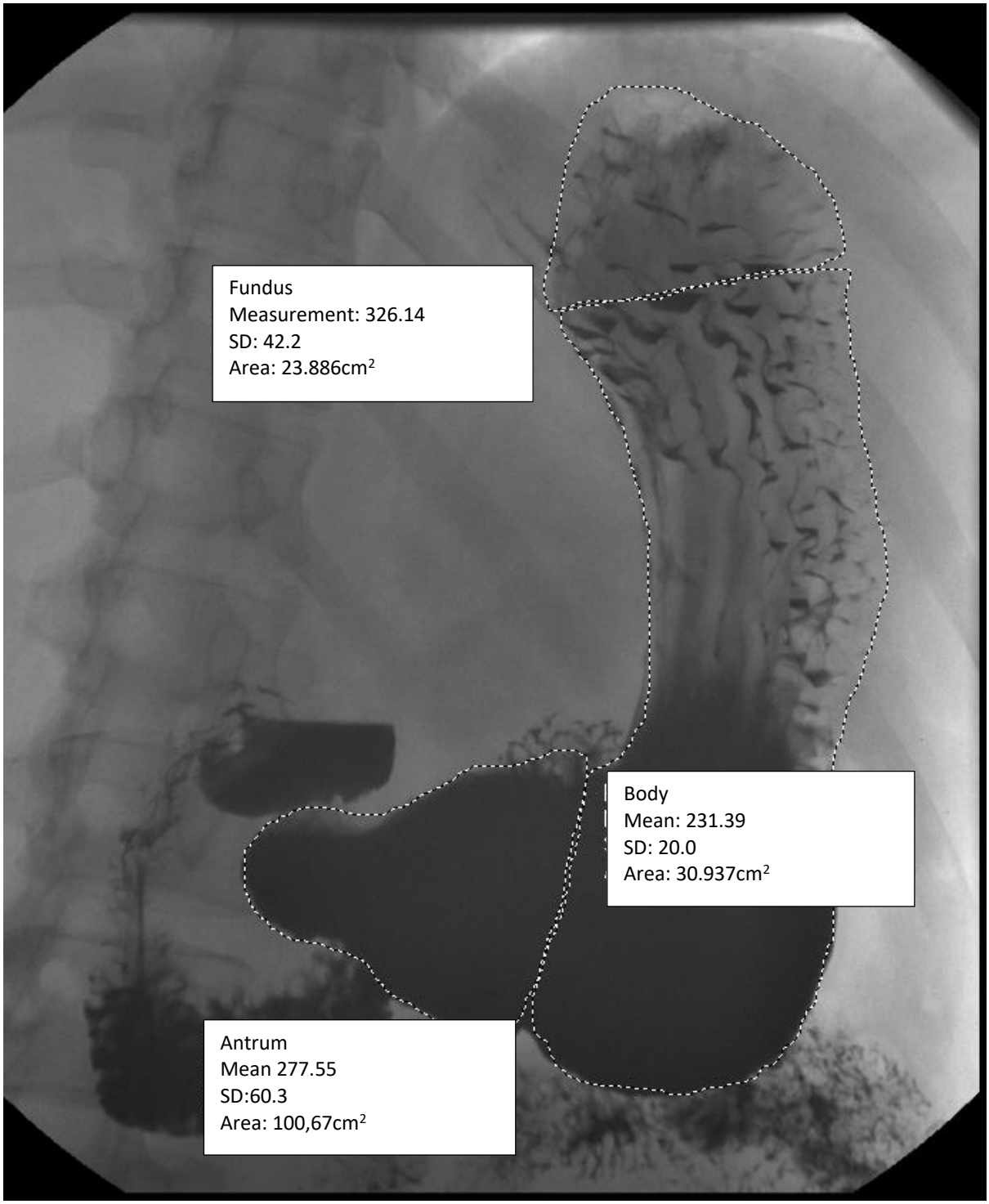
both these scenarios the NIH (Fletcher) risk score served as a favorable predictor. This is a useful tool in our setting, as our service has various shortcomings. Firstly, our facility does not offer routine mutational analysis due to cost. Tumours therefore cannot be genetically classified, subsequently the appropriateness of tyrosine kinase inhibitor prescription are not accurately targeted at diagnosis. Secondly, tyrosine kinase inhibitors are not available for all patients, requiring institutional motivation as to why the drug may benefit the specific patient. A high-risk NIH (Fletcher) score, now validated at our institution, will now serve as further motivation for the early use of Imatinib in these specific cases. We hope this will potentially improve outcomes and prevent tumour progression in these high-risk gastric GIST tumours.

Our novel findings warrant further investigation into the reasons as to why the proximal stomach appears to be favoured by GISTs. Specifically, the fundal GIST prevalence is of particular interest with our perception that tumours originating here potentially run a more aggressive course. In addition, the cost-benefit ratio between routine long-term tyrosine kinase administration for high-risk GISTs versus mutational analysis to determine if a tumour is indeed receptive to first-line treatment should be determined locally.

LIMITATIONS

Due to the rare prevalence of the tumor, increasing the sample size remains a challenge. Missing information due to historical nature of some of the folders resulted in 18 cases being excluded from the study. Our facility doesn't offer routine mutational analysis due to lack of funds and therefore this could not be included in this study, and standardization was based on mitotic counts.

Appendix 1:


Fundus
Measurement: 326.14
SD: 42.2
Area: 23.886cm2
Body
Mean: 231.39
SD: 20.0
Area: 30.937cm2
Antrum
Mean 277.55
SD:60.3
Area: 100,67cm2

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16 January 2020

HREC REF: 852/2019

Dr Gayla Chinnery
Dlvlslon of General Surgery
Upper GIT Surgery
UCT Private Academic Hospital

Dear Dr Chinnery

PROJECT TITLE: A RETROSPECTIVE AUDIT ON GROOTE SCHUUR'S GASTRIC GASTROINTESTINAL STROMAL TUMOURS PRESENTING TO GROOTE SCHUUR HOSPITAL (MMED DEGREE - DR SUZANNE KUHN)

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It Is a pleasure to inform you that the HREC has formally approved the above-mentioned study subject.

Approval Is granted for one year until the 30 January 2021.

Please submit a progress form, uslng the standardlsed Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study Is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

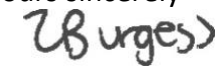
The HREC acknowledges that the student: Dr Suzanne Kuhn will also be Involved in this study.

Please note that for all studies approved by the HREC, the prlnclpal Investigator obtain approprlate Institutional approval, where necessary, before the research may occur.

Please note that the ongoing ethical conduct of the study remains the responslbility of the princlpal investigator.

Please quote the HREC REF in all your correspondence

Yours slncerely



PROFESSOR M BLOCKMAN

CHA*RPERSON. | HUMAN RESEARCH ETH*CS COMMITTEE

Federal WIde Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC Ref 852/2019
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NHREC-registration number: REC-210208-007

This serves to confirm that the Unlverslty of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patlents, based on the Medlcal Research Councll (MRC-SA), Food and Drug Adminlstratlon (FDA-USA), International Council for Harmonisatlon of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Cllnlcal Practice Guidelines (DOH 2006), based on the Association of the British Pharmaceutical Industry Guldellnes (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Commlttee granting this approval Is in compliance wlth the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

A Retrospective Audit on Gastric Gastrointestinal Stromal Tumours presenting to Groote Schuur Hospital

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Introduction

Gastrointestinal stromal tumors are the commonest mesenchymal tumor of the gastro intestinal tract. The have no predilection to a specific sex, and are most commonly found in t the 50+ age group.[1] They can present anywhere in the gastrointestinal tract, but most

common areas include stomach (50%) and small bowel(25%). 10% Of gastrointestinal stromal tumors present in the colon and rectum and another 10% in the mesentery, omentum, retroperitoneum and pelvis.[1]Risk factors and causative factor have not been identified. There is an increased risk in Neurofibromatosis type 1 and two other rare tumor syndromes (Carney's triad; Familial gastro intestinal tumor syndrome). [2]

Clinical presentation is non specific. Symptoms include early satiety, bloating, gastro intestinal bleeds and symptomatic anaemia.[3] Sometimes, small tumors are found incidentally on gastroscopy or during surgery.[3] Tumors typically metastasize to the liver and throughout the abdomen (serosal based lymph nodes). Extra abdominal spread is seen only in advanced disease, typically to the lungs and bone. [4]

Tumors vary in size from 10mm-350mm.[3] Gastrointestinal stromal tumors share many features with interstitial cells of Cajal-innervated cells, associated with Auerbach's plexus. [5] A popular hypothesis is that gastrointestinal stromal tumors arise from the interstitial cells of Cajal, or share a common stem cell type.[5]

Morphologically, the tumors fall into one of three groups: epitheloid, spindle cell or mixed type. The tumors can have large histological variation.[5]

Often, immunohistochemistry is necessary to confirm the diagnosis. GIST neoplasms expresses KIT protein and has the KIT or platelet derived growth factor receptor-alpha(PDGFRA) gene mutation. KIT, also called c-kit or CD117, is positive in 95%of GISTs by immunohistochemical staining, whereas 5% show low or no gene mutation.[6] DOG1, also known as ANO1, is positive in GIST, irrespective of expression of KIT, supporting the diagnosis of GIST[7]

Tumor size and mitotic activity are the two main prognostic factors as proposed by Fletcher and colleagues.[8] Tumor rupture, serosal invasion and a raised mitotic index (>10/50 HPF) has been identified as poor prognostic factors.(7)(6)Blood vessel invasion is a strong indicator of liver metastases.(7)

GIST tumors are often diagnosed incidentally on endoscopy or CT scan. Endoscopic ultrasound is very useful in locating lesions of the wall of the gastrointestinal tract.[9] CT and 18F-fl uoro-deoxyglucose PET are both useful for preoperative staging of such tumours. PET can reveal small metastases, which can later aid in the assessment of therapy effectiveness.[10]

Monitoring tumor response is a challenging problem in these patients. A reduction in size does not necessarily correlate with response. [11] Lesions either remain stable in size, or even increase in size due to intramural oedema or haemorrhage. [11] Generally, tumors will become hypocellular, with myxoid stroma and variable necrosis. [12] A quantitative decrease in standard uptake on PET scan can serve as an indicator of response. [13] The Canadian advisory committee on Gastrointestinal Stromal Tumours, recommend follow up CT imaging every 3-6 months for a minimum of 5 years post resection in pateints with residual disease. [14]

The main treatment of Gastrointestinal stromal tumors, is surgical resection. Pre operative biopsy is not recommended in highly suggestive tumors. Endoscopic fine needle aspiration or biopsy is the recommended methods of diagnosis in indeterminate tumors. [15]

In advanced disease, the median survival rate before commencement of the use of Imatinib, was 12-24 months. [1] However, the use of Imatinib in KIT positive tumors, has been proven effective. Imatinib, a tyrosine kinase inhibitor, reliably achieves disease control in 75-80% of patients with advanced disease. [11] Its structures mimics ATP, and acts by binding competitively to the binding sites of target kinases . [16] The median progression-free survival rate falls in the range of 20-24 months. [1] Patients who stop taking Imatinib before switching to new therapies can have rapid tumour growth, increased clinical symptoms and a tumour flare seen on PET scan. For this reason, patients who show a response to, or are stable with, imatinib should remain on treatment indefinitely, unless drug tolerance becomes an issue. [1]

Imatinib resistant tumors can be divided into two groups:

Primary resistance: Tumors that does not respond to Imatinib therapy within 6 months. These tumors most often have a KIT exon 9 mutation, or no detectable kinase mutation. They are morphologically similar to an undefined pleomorphic adenoma. [17]
Secondary resistance: Recurrence of tumor after 6 months of successful clinical response. Newly acquired kinase mutations are commonly seen in KIT (or PDGFRA). These mutations interfere with Imatinib activity in these patients. Secondary mutations is due to a population of tumour cells for which imatinib is cytostatic rather than cytocidal. Eradication of the stem cell of the tumor, might be the only medical cure for these tumors. [7]

The use of alternative kinase inhibitors (Sunitanib) has been approved in patients that show resistance to Imatinib therapy. [18] This has showed a decrease in disease progression. The use of neo adjuvant Imatinib therapy is currently researched in assisting with downsize of primary or metastatic disease prior to surgery. [18]

Aim:

The aim of this retrospective audit is to evaluate the diagnosis, management and outcomes of patients with gastric gastrointestinal stromal tumours presenting to Groote Schuur Hospital.

Objectives:

The primary objective is to review the incidence, presentation, diagnosis, surgical and oncological management of patients with gastric GISTs at Groote Schuur Hospital.

The secondary objectives are to evaluate complications of treatment, disease-free survival and overall survival related to histological subtype and tumour risk classification as regards subtype, size, position and mitotic count.

Methodology:

Study Design:

This will be a single center retrospective audit of patients with gastric GIST tumours presenting to the Upper Gastrointestinal Unit at Groote Schuur Hospital between 1st January

2015 and 31st September 2019. Patient demographics, presenting complaints, diagnostic investigations, surgical management and outcomes as well as tumour characteristics will be extracted from this database.

The use of neoadjuvant and adjuvant Imatinib therapy and dosing with subsequent tumour response, disease free survival and overall survival noted. This data will be extracted from the Upper Gastrointestinal Surgery Registry (HREC 031/2015). This database has recently been granted an extension until August 2021.

Characteristics of the study population:

Patient data that will be included has been captured as per ethical approval stipulated by the prior registration of the Upper GI Registry. Entry into this registry includes patients seen by the UGI surgical unit. Patients presenting with either malignant or benign gastric outlet obstruction will be selected out of this database.

Time Frame:

We aim to start this retrospective analysis of the database after DRC and HREC approval and include patients in the database from 1st January 2015 to 31st September 2019.

Research procedure and data collection methods:

From this data series, all patients with gastric GISTs will be selected from the approved registry. Individual patient folders will only be accessed via the Groote Schuur Hospital's Records Department should specific data be missing from the registry. At no stage will patients be contacted to obtain missing data.

Sample Size:

We anticipate approximately 80 - 100 patients from the registry to be included in this study.

Data collection:

The following data categories will be recorded:

- Patient factors:
  - Age
  - Sex
  - Co-morbidities
  - Presenting complaints
- Pre-operative workup:
  - Investigations performed
  - Tumour location, size and presence of metastases
- Surgery performed and development of any post-operative complications (as per Clavien-Dindo Classification)[4]
- Tumour histology and risk stratification with size, tumour position and mitotic count and grade noted as per NHLS report
- Oncology
  - Imatinib therapy and dosing
  - Follow up imaging and progression of disease
- Disease free survival, time to recurrence, overall survival and mortality

Data safety and monitoring:

A password protected computer-based registry has already been created for the approved database (HREC R031/2015; extension August 2021). Information extracted from patient folders, National Health Laboratory Services and PACS will be placed into a computer-based registry. Data safety and monitoring strategies will conform to those set for the collection and handling of data as per the approved Upper Gastrointestinal Surgery Registry. No paper-based data collection sheets will be used to record the data and analysis will take place directly from the registry whereby data will be exported to SPSS / Stata for statistical analysis.

To protect patient confidentiality:

Access to the registry is password protected and will only be accessed by investigators on this study. Data extracted from the registry as well as patient folders will be anonymized, and patient details will only be identifiable from their hospital folder number.

Research procedures and data collection methods:

All patients with histologically confirmed GIST on the database will be evaluated for potential inclusion in the study. Patients that proceeded to surgery will be eligible for inclusion as will those only treated with Imatinib. Individual patients folders will be accessed via the Groote Schuur Hospital's Records Department (located on the A floor in the New Main Building) and the investigated data will be extracted and placed into a spreadsheet. At no stage will the patients be contacted in order to obtain any missing data. Patients eligible for inclusion will have their staging CT accessed via the local PACS system by the investigators of this retrospective review. The immunohistochemistry will be confirmed on NHLS online access system.

Exclusion Criteria:

Patients on the database without histological confirmation of a gastric GIST will be excluded. Patients without imaging on the local PACS system will be excluded.

Data analysis:

All data exploration and analysis will be done in Stata (Version 13.1; Stata Corp, College Station, Texas USA). Descriptive statistics will be used to characterize the sample in terms of demographics, comorbidities, clinical presentation, investigations, surgery and histology. A $p<0.05$ will be considered statistically significant while 95% confidence intervals will be used to determine the precision of any estimates.

Ethical Considerations:

Patient data will be extracted retrospectively from an HREC approved database (HREC R031/2015; extension to August 2021) with no contact being made with the patients. There is no risk to this study as it is a retrospective registry review.

Patient confidentiality will be maintained, and the study will be conducted in accordance with the Helsinki Declaration.

Benefits of study:

This study aims to determine the incidence, management and outcomes of gastric GISTs for which a paucity of information is available as regards the South African population.

Risks to patients:

Nil.

Reimbursement for participation:

There will be no reimbursement for participants.

Budget:

No budget is required. There is no stationary cost to the division of Surgery as this data will be exclusively recorded on Redcap, freely available to UCT staff. We do not require any new computers to be purchased for this purpose.

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Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- Named authors’ consent to publication and meet the requirements of authorship as set out by the journal.
- The submission has not been previously published, nor is it before another journal for consideration.
- Any conflict of interest (or competing interests) as indicated by the author(s).
- A covering letter signed by ALL authors as a supplementary file.
- Written confirmation of Research Ethics Committee approval must be submitted as a supplementary file.
- Authors' details, including full names, current position, department and place of work, email addresses as well as ORCID as a supplementary file.

- The text complies with the stylistic and bibliographic requirements as per the Authors' Guidelines:

    - A style template is available under the Author Guidelines. The manuscript is in Microsoft Word format. The text is 1,5-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
    - Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG) and submitted as supplementary files.
    - Tables must be submitted as supplementary files (not included in the manuscript).

- Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID)
- An structured abstract or summary has been included where applicable.
- Please provide the names and email addresses of three possible reviewers for this manuscript.