Gastrointestinal stromal tumours in patients presenting to an academic hospital in South Africa

Authors:
Barbara M. Robertson[1]
Galya E. Chinnery[2]
Michael L. Locketz[3]
Michelle Parker[4]
Alvera A. Vorster[5]
Raj Ramesar[5]
Eugenio Panieri[2]
Alistair J. Hunter[1]

Affiliations:
[1]Department of Radiation Oncology, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

[2]Department of Surgery, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

[3]Division of Anatomical Pathology, National Health Laboratory Service, University of Cape Town, Cape Town, South Africa

[4]Department of Human Biology, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

[5]South African Medical Research Council, Genomic and Precision Medicine Research Unit, Division of Human Genetics, Department of Pathology, University of Cape Town, Cape Town, South Africa

Corresponding author:
Barbara Robertson,
barbara.robertson@uct.ac.za

Dates:
Received: 06 Jan. 2023
Accepted: 19 May 2023
Published: 13 June 2023

Background: Published information on African patients with gastrointestinal stromal tumours (GISTs) is limited.

Aim: The aim of this study was to review patient and tumour characteristics, and treatment, for a cohort of African patients and compare findings to studies from other centres.

Setting: Groote Schuur Hospital, South Africa.

Methods: Data were collected on all patients referred to Groote Schuur Hospital (GSH) during the period October 2003 to November 2019, including demographics, tumour characteristics and treatment outcomes.

Results: There were 124 patients in total. There was a slight male predominance (55.6%) and the median age was 56 years. The most common primary tumour sites were the stomach (66.2%) and small bowel (21.8%) with a median primary tumour diameter of 95.5 mm. Mutational analysis was conducted for 39 patients with 66.7% of these patients having mutations in *KIT* exon 11. The primary tumour was resected in 72 patients, with 48.6% having high-risk tumours according to the National Institutes of Health (NIH) risk assessment. The 10-year overall survival (OS) values for patients by risk group were 83% (very low and low risk), 73% (intermediate risk) and 66% (high risk). The disease control rate for patients treated with imatinib was 84.6%. The median progression-free survival (PFS) for patients treated with imatinib for palliation was 23 months with OS of 31 months.

Conclusion: In contrast to patients from other centres, our patients were younger and had larger tumours.

Contribution: The distribution of primary tumour site, mutational analysis and response to imatinib was consistent with the literature.

Keywords: gastrointestinal stromal tumours; Africa; treatment; imatinib; mutations; survival.

Introduction

Gastrointestinal stromal tumours (GISTs) have been recognised as distinct clinical and pathological entities for approximately 30 years. They are the most common sarcomas of the gastrointestinal tract (GIT) and can arise from any site in the GIT, including the mesentery and peritoneum, with the majority arising from the stomach. A small number are associated with germline mutations; however, the majority are sporadic. In 1998, it was established that mutations in the *KIT* gene were associated with GIST development, accounting for 75% – 80% of GISTs.[1] Approximately 6% of patients reported have mutations in the platelet-derived growth factor receptor alpha (*PDGFRA*) gene, while 10% – 15% of patients do not have known mutations and their tumours are classified as wild type.[2,3] However, for some of these wild-type tumours, mutations have been identified in the succinate dehydrogenase (SDH) gene complex, *NF1* and *BRAF*.[4]

Primary treatment of localised GISTs remains surgical resection. In patients with locally advanced or metastatic disease, standard initial treatment is with imatinib, a small molecule tyrosine kinase inhibitor. A phase II trial, followed by two phase III trials demonstrated that 70% – 80% of patients with unresectable disease had either a partial response or stable disease when treated with imatinib.[5,6,7] The mutational status determines the behaviour of the tumour as well as the response to treatment, with *KIT* exon 11 mutations responding more favourably to imatinib than the wild-type or those

with other *KIT* or *PDGFRA* mutations.[8] There is a paucity of published data on GISTs from the African continent. This study evaluated patient and tumour characteristics, treatment and treatment outcomes in a cohort of patients referred to Groote Schuur Hospital (GSH) and compared our African patients with published reports from other centres.

Patients and methods

Data collection

Groote Schuur Hospital is the academic hospital linked to the University of Cape Town (UCT) serving a population of approximately 4.5 million people. Data, including demographics, tumour characteristics and treatment for all patients with GISTs referred to the Department of Radiation Oncology at GSH during the period October 2003 to November 2019, were maintained on a password-protected database.

Treatment and follow-up

All patients were managed by a multidisciplinary team consisting of surgeons, clinical oncologists and pathologists. Diagnosis was confirmed on histology or cytology with baseline imaging by computerised axial tomography (CT) scanning. Tumour size was assessed either by the reporting pathologist if the tumour was resected with no prior treatment or by initial radiological measurements. Mitotic count was determined on the initial biopsy specimen if neoadjuvant or palliative imatinib was required.

Surgically fit patients with nonmetastatic GISTs were primarily resected. Patients with locally advanced disease were offered neoadjuvant imatinib to downstage the surgical resection requirements, with imatinib continued postoperatively. Before 2012, postoperative imatinib was not available for high-risk patients who had not received neoadjuvant imatinib. In the initial years of the study, the postoperative risk group was assigned based on the National Institutes of Health (NIH) risk assessment.[9] With time, additional available data allowed for the recurrence risk to be assessed by the nomogram described by Gold et al.,[10] as well as the prognostic contour maps proposed by Joensuu et al.[11] As such, after early 2012, patients with a probability of < 50% recurrence-free survival (RFS) were offered adjuvant imatinib for a period of 3 years. For the purpose of this study, the risk groups specified are according to the NIH risk assessment.

For patients with local disease who were not fit for a surgical procedure and patients with metastatic disease, primary treatment was imatinib. From 2004 to December 2014, imatinib was only available through the Glivec International Patient Assistance Program (GIPAP) administered by the Max Foundation, but since October 2015, imatinib has been provided by state hospital pharmacies.

Patients with the primary tumour resected were followed up and monitored for possible recurrence clinically and with CT scans at 6 monthly or annual intervals depending on the postoperative risk group. Recurrences in patients after curative surgery were assessed for repeat surgery, and if this was not possible, palliative imatinib was offered. For patients who received imatinib as initial treatment, response was monitored with a CT scan 3 months after starting treatment. As Response Evaluation Criteria in Solid Tumors (RECIST) criteria are difficult to apply to GIST, patients were assessed as having responded if lesions had decreased in size by at least 20% in greatest dimension or become cystic, whereas those tumours that remained the same size on the first CT at 3 months were assessed as having stable disease. Progression was defined as an increase of > 20% or the appearance of a new solid lesion. For patients receiving neoadjuvant imatinib, resection was performed as soon as the tumour was deemed resectable.

For patients with progressive disease on 400 mg imatinib daily, the dose was increased to 800 mg. Second-line sunitinib was available through the Sutent Patient Donation Program (SPAP) from December 2008 to late 2012. Since 2012, no second-line systemic treatment has been available for patients progressing on imatinib and these patients have continued to receive imatinib until treatment intolerance or death. Palliative radiation was offered to patients with symptomatic local disease not responding to imatinib and to those with bone metastases.

Routine mutational analysis was not available because of limited resources. However, funding was secured from UCT and Novartis, and mutational analysis was conducted for a small number of patients where tumour samples were available.

Histology slides for selected patients were retrieved from the archives of the Division of Anatomical Pathology at the GSH branch of the National Health Laboratory Service (NHLS)/UCT. The slides were reviewed by a histopathologist who confirmed the diagnosis and selected the single section with the largest continuous focus of viable tumour cells for each specimen. The area identified was circled on the haematoxylin and eosin (H&E) stained section. The corresponding formalin-fixed paraffin-embedded (FFPE) tissue block was obtained from archives. Eight sections of 5 μm thickness were cut with a clean, sterile microtome blade. These sections were heat fixed onto neutral-coated slides in an incubator at 37 °C for 45 min. Marked H&E stained slides and unstained sections were sent for mutational analysis. The procedure was initially performed by the Division of Human Genetics at UCT and subsequently by the Somatic Cell Genetics Unit, NHLS, Johannesburg.

Statistical analysis

For patients who had the primary tumour resected with curative intent, RFS was calculated from the time of first treatment, either imatinib or surgery, until documented recurrence. Overall survival (OS) for these patients was also calculated from the time of first treatment until death from

any cause. For patients treated with imatinib for palliative intent, progression-free survival (PFS) was calculated from the start of treatment with imatinib until evidence of progression or death, if no progression before death. Overall survival for these patients was calculated from the start of palliative imatinib until death from any cause. Disease control rate was calculated as the percentage of patients with measurable disease who had an initial response or stable disease when treated with imatinib. Statistical Package for Social Sciences (SPSS) version 27 (SPSS, Chicago, Illinois, United States) was used for statistical analyses. Survival curves were constructed using the Kaplan Meier method and compared using the log-rank test. A p-value of < 0.05 was accepted as significant.

Ethical considerations

The study was approved by the UCT Health Sciences Human Research Ethics Committee (HREC REF 375/2011). Written informed consent was obtained from all patients attending for follow-up.

Results

Patient and tumour characteristics

Patient and tumour characteristics are documented in Table 1. The total number of patients referred was 124. There was a slight male predominance and the median age was 56 years. Four patients had neurofibromatosis type I, while 15 (12%) patients had previously been treated, were currently receiving treatment or were subsequently diagnosed with other tumours, namely primary carcinomas of the prostate (n = 6), lung (n = 2), breast (n = 2), cervix (n = 1), stomach (n = 1), appendix (n = 1) and lymphoma (n = 3), with one patient having two different primary sites as well as GIST. Four patients were human immunodeficiency virus positive. Approximately 60% of the patients were performance status (PS) 0 or 1, with the majority (70%) having local disease at presentation. The most common organ of origin was the stomach followed by the small bowel. Approximately half of the resected patients were deemed to be of high postoperative risk score according to the NIH risk group. Mutational analysis was performed on 39 patients and the most common mutations were in *KIT* exon 11 with only two patients having mutations in *KIT* exon 9. One patient with a primary tumour in the stomach had mutations in *KIT* exon 17 and *PDGFRA* exon 12.

Treatment outcomes

The median overall follow-up period was 43 months. The median follow-up for patients treated with curative intent and for those treated with palliative intent was 66 and 26 months, respectively. Only four patients were lost to follow-up and censored at the last contact.

The primary tumour was resected with curative intent in 72 patients (58%) with a range of surgical procedures that are documented in Table 2. Of these 72 patients, 25 received treatment with imatinib as well. Thirteen required neoadjuvant treatment, of which 10 received both neoadjuvant and adjuvant treatment, and 12 received adjuvant treatment alone. Of the 13 patients requiring neoadjuvant imatinib, 12 had the primary site in the stomach and one in the rectum. The median time from the start of imatinib to surgery was 7 months. All patients who had required neoadjuvant imatinib were placed in the high-risk postoperative group by virtue of the preoperative primary tumour size, site or mitotic count. Of these patients, three did not continue with imatinib postoperatively because of imatinib unavailability or postoperative complications or, in one patient, there was the additional requirement for adjuvant treatment for breast carcinoma following simultaneous resection of a gastric GIST with a mastectomy. A further 12 patients with high-risk tumours did not receive adjuvant imatinib because of unavailability thereof. Treatment following recurrence included left hemi-hepatectomy (1 patient), palliative imatinib (11 patients) and supportive care (2 patients). The median survival time after tumour recurrence was 38 months.

Recurrence-free survival and OS were calculated for patients treated with curative intent according to postoperative risk group status. The RFS for both very low- and low-risk patients at 5 and 10 years was 100%. For intermediate-risk patients, the RFS at 5 and 10 years was 92% and 66%, respectively, and for high-risk patients, RFS was 73% and 66% for the same time intervals (Figure 1a). Because of the small number of patients in the very-low-risk group (n = 4), the OS for very low- and low-risk patients together was calculated to be 83% at both 5 and 10 years. For intermediate-risk patients, the OS at 10 years was 73%. The OS at 10 years for all high-risk patients was 66% (Figure 1b).

Recurrence-free survival was also calculated for high-risk patients comparing those who received adjuvant imatinib versus those who did not and was found not to be significant (p = 0.433). For patients who received adjuvant imatinib, the RFS at 5 years was 79% versus 66% for those who did not, and at 10 years RFS was 63% for adjuvant imatinib versus 66% for no adjuvant therapy (Figure 2a).

There was a trend for the OS for high-risk patients who received adjuvant imatinib to be higher than for those who did not receive adjuvant imatinib. However, the difference was not found to be significant (p = 0.19). The OS at 10 years for these groups was 76% and 54%, respectively (Figure 2b).

There was no difference in the OS for patients with R0 versus R1 resections (p = 0.62). The OS for all R0 patients was 84% and 71% at 5 and 10 years, respectively, and for R1 patients 79% for both time periods. If patients with tumour rupture were excluded, the OS was also not significantly different for R0 and R1 resections (p = 0.56) (Figure 3).

Fifteen patients presented with local disease and did not have surgery for the following reasons: not fit for surgery

TABLE 1: Patient and tumour characteristics.

Characteristic	Median	Range	Number	%
Gender				
Male	-	-	69	55.6
Female	-	-	55	44.3
Age	56	14–85	-	-
Country of origin				
South Africa	-	-	116	93.5
Zimbabwe	-	-	5	4.0
Angola	-	-	1	0.8
Malawi	-	-	1	0.8
Nigeria	-	-	1	0.8
Performance status				
0	-	-	14	-
1	-	-	58	-
2	-	-	32	-
3	-	-	19	-
4	-	-	1	-
Stage at presentation				
Local	-	-	87	70.0
Metastatic	-	-	37	30.0
Primary site of tumour				
Stomach	-	-	82	66.2
Small bowel	-	-	27	21.8
Rectum	-	-	5	4.0
Mesentery	-	-	3	2.4
Anus	-	-	1	0.8
Oesophagus	-	-	1	0.8
Peritoneum	-	-	1	0.8
Colon	-	-	1	0.8
Unknown	-	-	3	2.4
Median largest tumour diameter	95.5	1–370	-	-
CD117 (kit receptor) positive	-	-	118	95.0
DOG1 positive (on 35 samples tested)	-	-	35	100.0
Morphology				
Spindle	-	-	84	67.8
Epithelioid	-	-	11	8.9
Mixed	-	-	26	20.9
Unknown	-	-	3	2.4
Mitotic count				
≤ 5/50 HPF	-	-	81	65.3
> 5/50 HPF	-	-	12	9.7
> 10/50 HPF	-	-	25	20.2
Unknown	-	-	6	4.8
Postoperative risk group for 72 patients with primary tumour resected				
Very low	-	-	4	5.5
Low	-	-	14	19.4
Intermediate	-	-	18	25.0
High	-	-	35	48.6
Unknown	-	-	1	1.4
Mutations in 39 patients (percentage of known mutations)				
KIT exon 11 deletion	-	-	17	43.6
KIT exon 11 substitution	-	-	9	23.1
KIT exon 9	-	-	2	5.1
PDGFRA exon 18	-	-	2	5.1
KIT exon 17 and *PDGFRA* 12	-	-	1	2.6
KIT exon 11 and *KIT* exon 17 substitutions	-	-	1	2.6
Wild type	-	-	7	17.6

PDGFRA, platelet-derived growth factor receptor alpha; HPF, response evaluation criteria in solid tumors.

TABLE 2: Surgical procedures in 72 patients operated with curative intent.

Primary site	Surgical procedure	Number
Stomach	Wedge resection	34
	Distal gastrectomy	5
	Total gastrectomy	2
	Total gastrectomy plus multiorgan resection	6
	Wedge resection plus resection liver metastasis	1
Small bowel	Segmental resection	18
Peritoneum/mesentery	Resection	3
Rectum	Local excision	2
	Anterior resection	1

primary tumour (*n* = 1), treatment refusal or presentation in a preterminal state (*n* = 2).

The disease control rate for imatinib was calculated for patients who had measurable disease, specifically those with locally advanced disease requiring neoadjuvant imatinib who proceeded to surgery and those treated with palliative intent. The total number of patients in this group was 65; 55 had either an initial response to treatment or stable disease at 3 months leading to a control rate of 84.6%. For the remaining ten patients, five had documented progression on treatment, four died with no response assessment and one was lost to follow-up.

A total of 52 patients were treated with palliative intent from the initial diagnosis. These included those who presented with metastatic or unresectable local disease that did not proceed to curative surgery (*n* = 44) and those with a local disease who had significant comorbidities precluding surgery (*n* = 8). Of the 52 patients, 45 received imatinib. The remaining seven patients either presented in a preterminal state (*n* = 3) or declined treatment (*n* = 4). The median PFS of patients treated with 400 mg imatinib for palliation was 20.5 months (Figure 4a).

Twenty-five patients had the dose of imatinib increased to 800 mg daily with median PFS on the increased dose of 3.5 months. Only two patients received sunitinib through the SPAP. One patient had stable disease for 10 months and the other died within 2 months of commencing treatment. The median OS for patients treated palliatively with imatinib was 36 months (Figure 4b).

Four patients were treated with palliative external beam radiation. One patient received 20 Gray (Gy) in four fractions to a peritoneal metastasis, achieved partial response and had stable disease for a period of 11 months. Two patients received palliative radiation for painful vertebral metastases and one for persistent bleeding from an unresectable gastric GIST.

The 27 patients with known mutations who received imatinib were evaluated for response to treatment. The reasons for prescribing imatinib included neoadjuvant for initially unresectable local disease (*n* = 5), adjuvant for high-risk tumours (*n* = 8) and palliation (*n* = 14). All those with *KIT* exon 11 mutations (*n* = 20) had an initial response, stable disease or did not progress on adjuvant imatinib.

because of significant comorbidities (*n* = 8), no response/ progression on imatinib (*n* = 3), death because of imatinib toxicity (*n* = 1), concurrent metastatic disease from another
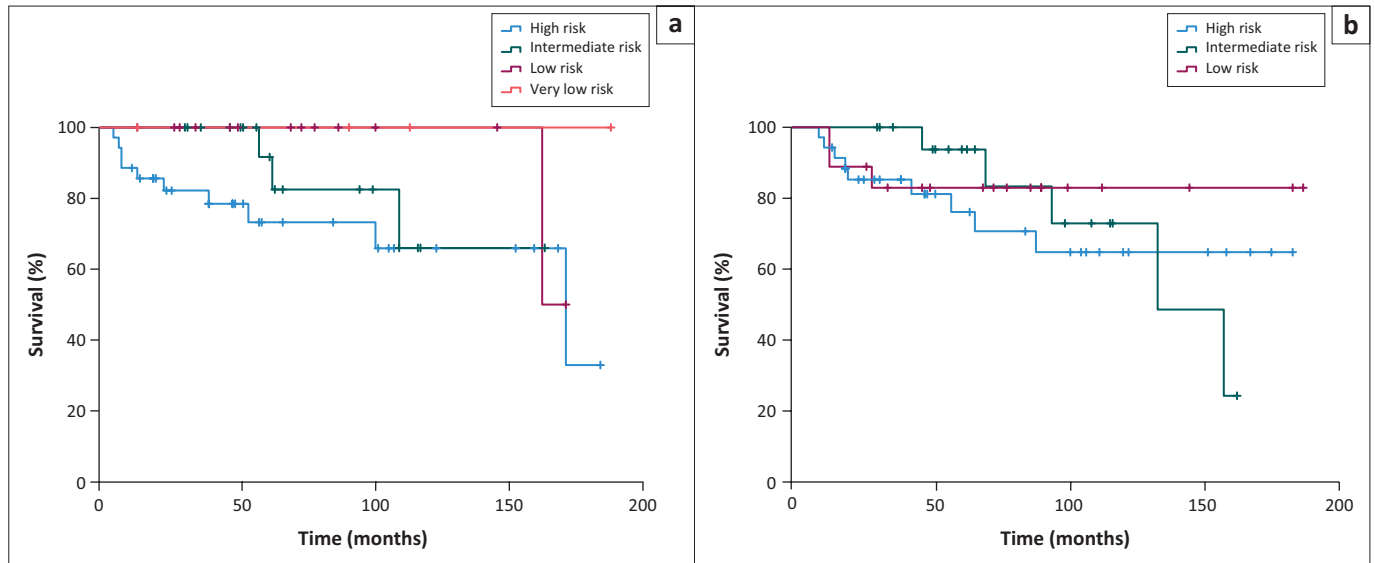
FIGURE 1: (a) Recurrence-free survival for high-, intermediate-, low- and very-low-risk groups. (b) Overall survival for high-, intermediate- and low-risk groups. The very low-risk patients were incorporated into the low-risk category.
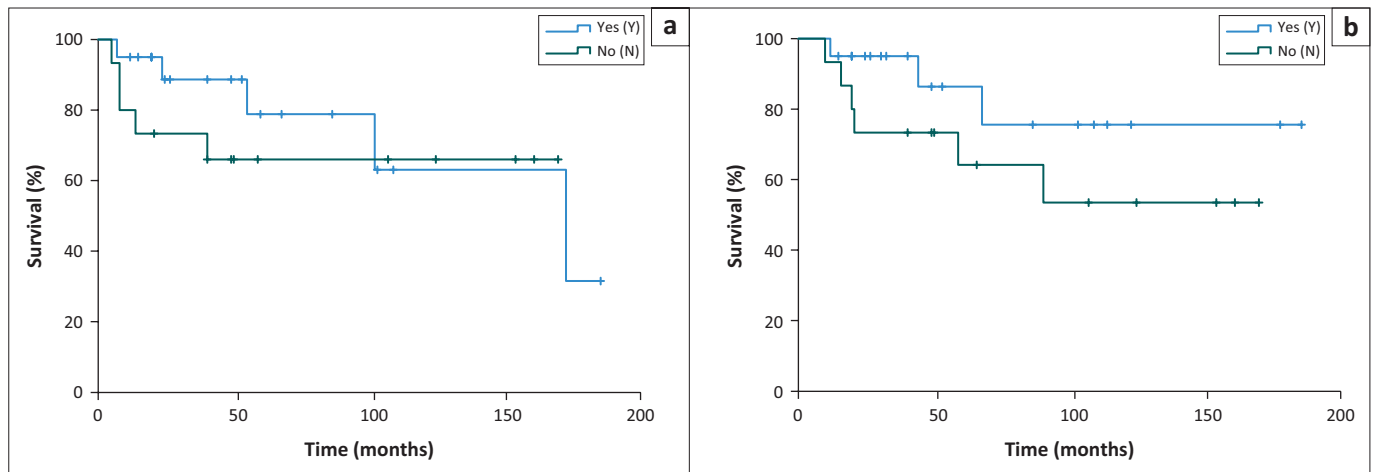

FIGURE 2: (a) Recurrence-free survival for high-risk patients; adjuvant imatinib (Y) versus no imatinib (N). (b) Overall survival for high-risk patients; adjuvant imatinib (Y) versus no imatinib (N).
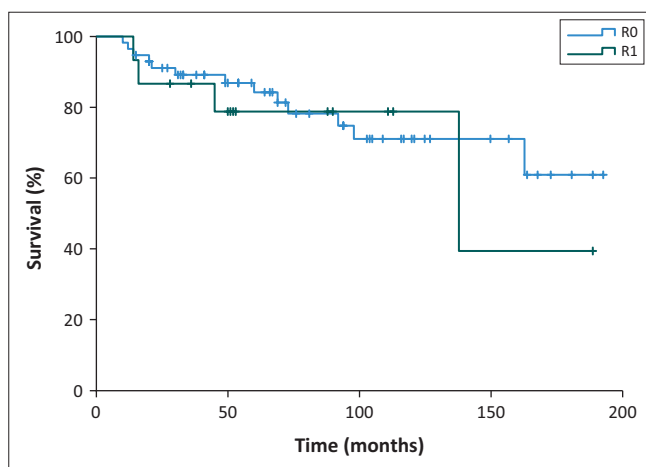

FIGURE 3: Overall survival for R0 versus R1 resections. Patients with tumour rupture were included.

Of the four patients with wild-type tumours that received imatinib, one responded to treatment and died of metastatic adenocarcinoma of the prostate, one with neurofibromatosis did not respond, one received adjuvant treatment and remains alive and clear and the response of the fourth patient is unknown. Two patients with *KIT* exon 9 mutations received imatinib, one for palliation who progressed 9 months after starting treatment on 400 mg and one for adjuvant treatment who remains alive and clear of disease 4 years after surgery. One patient with a *PDGFRA* exon 18 mutation had a high-risk tumour, received adjuvant imatinib (the mutation was identified only after starting treatment) and died of a cause unrelated to GIST.

Treatment toxicity

In general, imatinib was well tolerated with most toxicities scored as grade 1 to 2 (Table 3). The most common toxicities were oedema, nausea, anaemia, vomiting, fatigue and diarrhoea. Adjuvant treatment was stopped in two patients because of grade 3 liver toxicity and grade 3 neutropenia that persisted after dose reduction. The other grade 3 toxicities noted were oedema, anaemia, fatigue and neutropenia. Dose reductions were required in seven patients. One
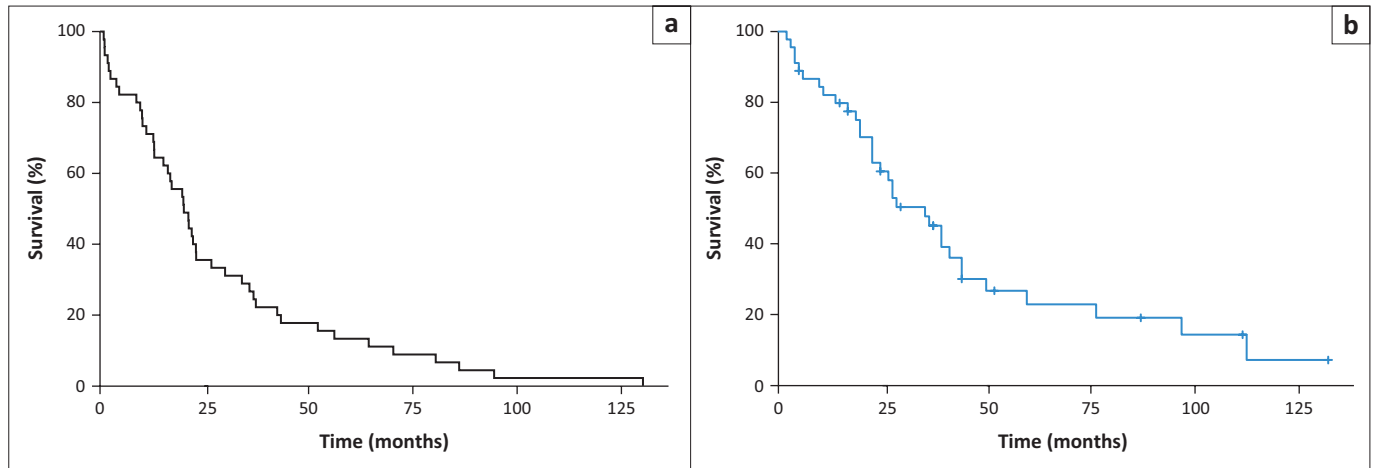
FIGURE 4: (a) Progression-free survival for palliative patients treated with imatinib (400 mg). (b) Overall survival for palliative patients treated with imatinib (400 mg).

TABLE 3: Adverse events related to imatinib.

Adverse event	Grade				
	1	2	3	4	5
Oedema	33	4	1	0	0
Nausea	35	1	0	0	0
Vomiting	19	1	0	0	0
Dry skin	4	0	0	0	0
Anaemia	8	11	2	0	0
Fatigue	15	2	1	0	0
Diarrhoea	16	1	0	0	0
Hypopigmentation	1	5	0	0	0
Musculoskeletal	10	0	0	0	0
Neutropenia	4	4	4	0	0
Abnormal liver functions	3	0	1	0	0
Dizziness	1	0	0	0	0
Memory impairment	1	0	0	0	0
Erythroderma	0	0	0	0	1

patient passed away because of postoperative complications with two further patients dying from sepsis following local procedures for disease control. A further patient developed fatal erythroderma 2 months after starting imatinib.

Discussion

In this review of 124 African patients with GIST referred to an academic hospital, we noted many similarities in patient and tumour characteristics with regard to primary site and mutational analysis when compared to previously published cohorts of patients from outside Africa. Efficacy of imatinib was also confirmed in our population with 84.6% of patients who received imatinib either having a response or stable disease. The median age of 56 years was, however, younger than expected with median ages reported between 60 and 66 years from other centres.[12,13,14,15,16,17,18,19] It is known that patients with GIST often have other cancers, possibly because of demographic, genetic or environmental factors. In the present study, additional cancers were present in 12% of patients, the most common being adenocarcinoma of the prostate. Similarly, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database,[20] 17.1% of patients with GIST had other primary sites while in a study from Germany 43% of patients had other malignancies.[21]

The distribution of primary sites was as expected with the stomach being the most common (66.2%) followed by the small bowel (21.8%). Of the four patients with neurofibromatosis type 1, three had the primary site in the small bowel and for the fourth patient the primary site was uncertain. Most patients presented with large tumours, with 77% having tumours larger than 50 mm with the median tumour diameter being 95 mm. Additionally, larger tumour size led to the categorisation of 80% of patients as a high-risk postoperative group indicating that the majority of our patients presented with advanced disease. On review of the literature, other centres have reported median tumour sizes ranging from 45 to 80 mm.[14,15,16,22] Although 87 (70%) patients presented with local disease, only 72 (58% of the entire cohort) had surgery with curative intent. The postoperative group with the highest percentage of patients was the high-risk group (48.6%). Other centres have reported between 26.7% and 53.3% of patients having high-risk tumours.[13,16,17,18,23,24,25,26,27] The percentage of our patients who had metastases at diagnosis (30%) is also higher than the literature where percentages ranging from 10% to 18% have been reported.[28,29,30]

A previous paper on mutations in South African patients with GIST reported a lower incidence of *KIT* exon 9 mutations.[31] However, for the 39 patients for whom mutational analysis was available in the present study, the distribution of mutations was consistent with international data. The most common mutations were in *KIT* exon 11 (66.7%), while 17.9% were wild-type including two of the patients with neurofibromatosis.[19,28,30,32] SDHB was analysed for one patient with a wild-type tumour but was found to be intact. While mutations in *KIT* and *PDGFRA* are generally described as being mutually exclusive, one patient was found to have mutations in both. A centre in Korea also reported four patients with double mutations in *KIT* and *PDGFRA*.[33]

Adjuvant treatment with imatinib is standard for patients with tumours with a high risk of recurrence as the results of the Scandinavian Sarcoma Group (SSG XVIII/ Arbeitsgemeinschaft Internistische Onkolgie [AIO]) trial

showed significant improvement in both RFS and OS for patients treated with imatinib for 3 years compared with 1 year.[34] In addition, two trials have shown improvement in RFS when compared to observation postoperatively.[35,36] The 10-year RFS of 63% for our high-risk patients who received adjuvant imatinib compares favourably with that of the SSG XVIII/AIO and the European Organisation for Research and Treatment of Cancer (EORTC) 62024 trials where the 10-year RFS were 52.4% and 62.5%, respectively, for adjuvant imatinib.[34,36] The 10-year OS of 76% for our high-risk patients who received 3 years of adjuvant imatinib was slightly lower than the 81.6% 10-year survival reported in the SSG XVIII/AIO trial.[34] However, while the SSG XVIII/AIO trial found a significant difference in favour of 3 versus 1 year of imatinib for both RFS and OS, for our patients, there was no significant difference in either RFS or OS for those who received adjuvant imatinib compared to those who did not. This may, however, be related to the small number of patients. The 5-year OS of 79% for high-risk patients who did not receive imatinib also compares favourably with other centres where survival rates range from 20.3% to 72.1% at 5 years.[17,37] Of the 15 patients with high-risk tumours who did not receive adjuvant imatinib, 7 remain alive and clear of disease and 2 died of causes unrelated to GIST. The OS of 83% at 5 years for the very low- and low-risk patients and 94% for the intermediate-risk patients compares favourably with the literature where OS of 80% – 100% for these groups has been reported.[17,24,26]

For the patients in this study, there was no difference in OS for patients who had R0 versus R1 resections. This is supported by a previous analysis of 908 patients randomised to 2 years of adjuvant imatinib or observation following resection of intermediate- or high-risk GIST where no difference in OS could be demonstrated once patients with tumour rupture were excluded.[38]

On further evaluation of the patients who developed recurrence, seven patients recurred within 2 years of surgery and a further seven between 4 and 15 years after surgery. For the seven patients who recurred within 2 years, all had tumours with high-risk features, and for six of these, imatinib was either not available at the time or there was a delay in prescribing imatinib because of postoperative complications. For the one patient who did receive adjuvant imatinib, there was recurrence on treatment. Of the seven patients who developed recurrence more than 4 years after surgery, two completed 3 years of adjuvant imatinib and recurred 4.5 and 15 years after surgery, respectively, and two did not complete adjuvant imatinib. Of the remaining three patients who developed late recurrences, two had low- and intermediate-risk tumours and for one the risk group was unknown; none of these patients had received adjuvant imatinib. Although there are no definitive data for optimal follow-up of patients treated with curative intent, our findings suggest that surveillance for recurrence should continue for longer than 5 years as late recurrence is possible even in low-risk tumours.

The median PFS of 20.5 months for the 45 patients treated with imatinib for palliation is similar to the results of the Gastrointestinal Stromal Tumor Meta-Analysis group of the two trials conducted to compare the standard dose with a higher dose of imatinib (MetaGIST project) where the PFS for all patients on both trials was 1.58 years (18.96 months).[39] However, the median OS of 36 months for our patients was shorter than the 4.08 years reported in these trials in spite of our patients having access to higher doses of imatinib. The long-term results of the EORTC, Italian Sarcoma Group and Australasian Gastrointestinal Trials Group trial reported that smaller tumour size and PS were prognostic for long-term survival.[40] The median primary tumour size of our patients treated with imatinib with palliative intent was 132 mm and 26 (58%) were PS 2 and 3. Large tumour size and poor PS could therefore have been factors for the lower-than-expected OS.

In summary, this cohort of African patients with GIST shows similar characteristics to patients from other regions of the world with regard to the primary site, distribution of mutations in the patients tested, outcomes in those treated with curative intent as well as response to imatinib. The age at presentation was, however, younger and patients presented with more advanced disease as reflected by the size of the primary tumour, the number of patients in the high-risk postoperative group and the percentage of patients presenting with metastases. We also noted that recurrence can occur later than the recommended follow-up period and that recurrence is possible even in low-risk tumours. Although the PFS for palliative treatment with imatinib was similar to the MetaGIST project, the OS was lower for our patients and was probably related to greater tumour burden. We postulate that advanced disease at presentation, specifically the size of the primary tumour and the percentage of patients with metastases, is because of delayed diagnosis rather than tumour biology.

Acknowledgements

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

B.M.R. designed the project, collected, analysed and interpreted the data and drafted the manuscript. G.E.C. and

Data availability

The data that support the findings of this study are available on request from the corresponding author, B.M.R. The data are not publicly available because of the potential to compromise the privacy of research participants.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

References

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of *c-kit* in human gastrointestinal stromal tumors. Science. 1998;279(5350):577–580. https://doi.org/10.1126/science.279.5350.577

2. Heinrich MC, Corless CL, Duensing A, et al. *PDGFRA* activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708–710. https://doi.org/10.1126/science.1079666

3. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125(3):660–667. https://doi.org/10.1016/S0016-5085(03)01046-1

4. Boikos SA, Pappo AS, Killian JK, et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: A report from the National Institutes of Health gastrointestinal stromal tumor Clinic. JAMA Oncol. 2016;2(7):922–928. https://doi.org/10.1001/jamaoncol.2016.0256

5. Demetri GD, Von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472–480. https://doi.org/10.1056/NEJMoa020461

6. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: Randomised trial. Lancet. 2004;364(9440):1127–1134. https://doi.org/10.1016/S0140-6736(04)17098-0

7. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol. 2008;26(33):5360–5367. https://doi.org/10.1200/JCO.2008.17.4284

8. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008;26(4):626–632. https://doi.org/10.1200/JCO.2007.13.4452

9. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459–465. https://doi.org/10.1053/hupa.2002.123545

10. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: A retrospective analysis. Lancet Oncol. 2009;10(11):1045–1052. https://doi.org/10.1016/S1470-2045(09)70242-6

11. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: An analysis of pooled population-based cohorts. Lancet Oncol. 2012;13(3):265–274. https://doi.org/10.1016/S1470-2045(11)70299-6

12. Soreide K, Sandvik OM, Soreide JA, Gudlaugsson E, Mangseth K, Haugland HK. Tyrosine-kinase mutations in c-KIT and PDGFR-alpha genes of imatinib naive adult patients with gastrointestinal stromal tumors (GISTs) of the stomach and small intestine: Relation to tumour-biological risk-profile and long-term outcome. Clin Transl Oncol. 2012;14(8):619–629. https://doi.org/10.1007/s12094-012-0851-x

13. Yang ML, Wang JC, Zou WB, Yao DK. Clinicopathological characteristics and prognostic factors of gastrointestinal stromal tumors in Chinese patients. Oncol Lett. 2018;16(4):4905–4914. https://doi.org/10.3892/ol.2018.9320

14. Chan KH, Chan CW, Chow WH, et al. Gastrointestinal stromal tumors in a cohort of Chinese patients in Hong Kong. World J Gastroenterol. 2006;12(14):2223–2228. https://doi.org/10.3748/wjg.v12.i14.2223

15. Tryggvason G, Gislason HG, Magnusson MK, Jonasson 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):289–293. https://doi.org/10.1002/ijc.21167

16. Bertolini V, Chiaravalli AM, Klersy C, et al. Gastrointestinal stromal tumors – Frequency, malignancy, and new prognostic factors: the experience of a single institution. Pathol Res Pract. 2008;204(4):219–233. https://doi.org/10.1016/j.prp.2007.12.005

17. Rubio J, Marcos-Gragera R, Ortiz MR, et al. Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur J Cancer. 2007;43(1):144–148. https://doi.org/10.1016/j.ejca.2006.07.015

18. Li CF, Chuang SS, Lu CL, Lin CN. Gastrointestinal stromal tumor (GIST) in southern Taiwan: A clinicopathologic study of 93 resected cases. Pathol Res Pract. 2005;201(1):1–9. https://doi.org/10.1016/j.prp.2004.11.002

19. Joensuu H, Rutkowski P, Nishida T, et al. *KIT* and *PDGFRA* mutations and the risk of GI stromal tumor recurrence. J Clin Oncol. 2015;33(6):634–642. https://doi.org/10.1200/JCO.2014.57.4970

20. Murphy JD, Ma GL, Baumgartner JM, et al. Increased risk of additional cancers among patients with gastrointestinal stromal tumors: A population-based study. Cancer. 2015;121(17):2960–2967. https://doi.org/10.1002/cncr.29434

21. Vassos N, Agaimy A, Hohenberger W, Croner RS. Coexistence of gastrointestinal stromal tumours (GIST) and malignant neoplasms of different origin: Prognostic implications. Int J Surg. 2014;12(5):371–377. https://doi.org/10.1016/j.ijsu.2014.03.004

22. Wozniak A, Rutkowski P, Piskorz A, et al. Prognostic value of *KIT/PDGFRA* mutations in gastrointestinal stromal tumours (GIST): Polish Clinical GIST Registry experience. Ann Oncol. 2012;23(2):353–360. https://doi.org/10.1093/annonc/mdr127

23. Hashmi AA, Faraz M, Nauman Z, et al. Clinicopathologic features and prognostic grouping of gastrointestinal stromal tumors (GISTs) in Pakistani patients: An institutional perspective. BMC Res Notes. 2018;11(1):457. https://doi.org/10.1186/s13104-018-3562-8

24. Hatipoglu E, Demiryas S. Gastrointestinal stromal tumors: 16 years' experience within a university hospital. Rev Esp Enferm Dig. 2018;110(6):358–364. https://doi.org/10.17235/reed.2018.5199/2017

25. Peixoto A, Costa-Moreira P, Silva M, et al. Gastrointestinal stromal tumors in the imatinib era: 15 years' experience of a tertiary center. J Gastrointest Oncol. 2018;9(2):358–362. https://doi.org/10.21037/jgo.2017.11.11

26. Ahmed I, Welch NT, Parsons SL. Gastrointestinal stromal tumours (GIST) – 17 years experience from Mid Trent Region (United Kingdom). Eur J Surg Oncol. 2008;34(4):445449. https://doi.org/10.1016/j.ejso.2007.01.006

27. Wang M, Xu J, Zhao W, et al. Prognostic value of mutational characteristics in gastrointestinal stromal tumors: A single-center experience in 275 cases. Med Oncol. 2014;31(1):819. https://doi.org/10.1007/s12032-013-0819-x

28. Emile JF, Brahimi S, Coindre JM, et al. Frequencies of *KIT* and *PDGFRA* mutations in the MolecGIST prospective population-based study differ from those of advanced GISTs. Med Oncol. 2012;29(3):1765–1772. https://doi.org/10.1007/s12032-011-0074-y

29. Tryggvason G, Kristmundsson T, Orvar K, Jonasson JG, Magnusson MK, Gislason HG. Clinical study on gastrointestinal stromal tumors (GIST) in Iceland, 1990–2003. Dig Dis Sci. 2007;52(9):2249–2253. https://doi.org/10.1007/s10620-006-9248-4

30. Braconi C, Bracci R, Bearzi I, et al. *KIT* and *PDGFRalpha* mutations in 104 patients with gastrointestinal stromal tumors (GISTs): A population-based study. Ann Oncol. 2008;19(4):706–710. https://doi.org/10.1093/annonc/mdm503

31. Baker G, Babb C, Schnugh D, et al. Molecular characterisation of gastrointestinal stromal tumours in a South African population. Oncol Lett. 2013;5(1):155–160. https://doi.org/10.3892/ol.2012.1013

32. Tryggvason G, Hilmarsdottir B, Gunnarsson GH, Jonsson JJ, Jonasson JG, Magnusson MK. Tyrosine kinase mutations in gastrointestinal stromal tumors in a nation-wide study in Iceland. APMIS. 2010;118(9):648–656. https://doi.org/10.1111/j.1600-0463.2010.02643.x

33. Kim JH, Ryu MH, Yoo C, et al. Long-term survival outcome with tyrosine kinase inhibitors and surgical intervention in patients with metastatic or recurrent gastrointestinal stromal tumors: A 14-year, single-center experience. Cancer Med. 2019;8(3):1034–1043. https://doi.org/10.1002/cam4.1994

34. Joensuu H, Eriksson M, Sundby Hall K, et al. Survival outcomes associated with 3 years vs 1 year of adjuvant imatinib for patients with high-risk gastrointestinal stromal tumors: An analysis of a randomized clinical trial after 10-year follow-up. JAMA Oncol. 2020;6(8):1241–1246. https://doi.org/10.1001/jamaoncol.2020.2091

35. DeMatteo RP, Ballman KV, Antonescu CR, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Ann Surg. 2013;258(3):422–429. https://doi.org/10.1097/SLA.0b013e3182a15eb7

36. Casali PG, Le Cesne A, Velasco AP, et al. Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST) from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (ISG), and Spanish Group for Research on Sarcomas (GEIS)(). Ann Oncol. 2021;32(4):533–541. https://doi.org/10.1016/j.annonc.2021.01.004

37. Wang M, Xu J, Zhang Y, et al. Gastrointestinal stromal tumor: 15-years' experience in a single center. BMC Surg. 2014;14:93. https://doi.org/10.1186/1471-2482-14-93

38. Gronchi A, Bonvalot S, Poveda Velasco A, et al. Quality of surgery and outcome in localized gastrointestinal stromal tumors treated within an international intergroup randomized clinical trial of adjuvant imatinib. JAMA Surg. 2020;155(6):e200397. https://doi.org/10.1001/jamasurg.2020.0397

39. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: A meta-analysis of 1,640 patients. J Clin Oncol. 2010;28(7):1247–1253. https://doi.org/10.1200/JCO.2009.24.2099

40. Casali PG, Zalcberg J, Le Cesne A, et al. Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumors: Long-term analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels. J Clin Oncol. 2017;35(15):1713–1720. https://doi.org/10.1200/JCO.2016.71.0228