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GENERAL SURGERY

Spectrum and surgical outcomes of gastrointestinal stromal tumours

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Background: Surgery and imatinib are the mainstays of the management of gastrointestinal stromal tumours (GIST). This study aimed to analyse the outcomes in the management of GIST utilising surgery and imatinib.
Methods: Progression-free survival (PFS) and overall survival (OS) were analysed in relation to imatinib therapy, location of tumour, resection margins, type and extent of surgery. Imatinib was administered in the neoadjuvant (maximum 12 months) and adjuvant setting (minimum 36 months) and until disease progression or drug intolerance. Disease response was assessed with the Choi criteria. Survival analysis included calculation of PFS, OS and Kaplan–Meier curves.
Results: Sixty-two patients were reviewed and 56 had surgical resection. The median age (range) was 58.5 (8–95) years. The median PFS and OS (IQR) was 24.0 (0–52.0) and 41.0 (15.0–74.0) months, respectively. Thirty-nine (70%) patients were treated with imatinib, with 21 of these in a neoadjuvant setting. In the patients undergoing surgery, surgical margins were R0, R1 and R2 in 41 (75%), eight (15%) and six (11%) respectively. There was an insignificant difference in the overall survival in these three groups. For those having liver metastasectomy and multivisceral resection, the PFS and OS were 32.5 (17.5–60.3) and 28.5 (5.75–49.8) ($p = 0.008$), and 96.0 (58.5–116) and 80 (50.5–92.3) months ($p = 0.033$), respectively.
Conclusion: Whilst the numbers were small, certain trends were observed. Surgery in combination with imatinib offers survival benefit in patients undergoing R0, R1, R2, liver metastases and multivisceral resections.
Keywords: gastrointestinal stromal tumours, irresectable tumour, metastatic tumour, tyrosine kinase receptor, c-kit mutation, platelet-derived growth factor receptor alpha gene, imatinib, target therapy, overall survival, disease-free survival, primary resection, multivisceral resection

Introduction

Gastrointestinal stromal tumours (GIST) arise from the interstitial cells of Cajal which are essential to motility of the gastrointestinal tract. These cells as well as GIST cells stain for the c-kit tyrosine kinase receptor which transmits signals from the cell membrane into the cell by way of signal transduction.[1] Although rare, GISTs are the most common mesenchymal tumours in the digestive tract, and the stomach is the most frequent site followed by the small bowel. The colon and oesophagus comprise less than 10% of these tumours.[2] Most GISTs are a consequence of mutation in c-kit gene or platelet-derived growth factor receptor alpha gene, but up to 5% do not have these mutations and are referred to as wild types.[2] Prior to the advent of imatinib, surgery resulted in a 5-year survival that exceeded 50% and this was not influenced by microscopic surgical margins suggesting that there was similar survival between R0 and R1 resection margins.[3] In another report on 55 patients with a 75% 5-year survival of macroscopically resection of GISTs, the prognosis was negatively affected by a > 10 mitoses per 50 high power fields and resection margins with R0 resection improving survival.[4] Recurrence of tumour occurred at a mean time of 21 ± 10 (range 4–36 months).

The discovery of imatinib, a small molecule tyrosine kinase inhibitor for the treatment of a tumour which was resistant to radiotherapy and chemotherapy resulted in a significant improvement in the management of these tumours. It was initially approved for use in metastatic disease then recurrent disease, and finally it was found to be effective in both the neoadjuvant and adjuvant settings resulting in long-term survival.[5]

A meta-analysis of imatinib therapy comparing different dosing regimens, the 800 mg daily dose had a slight (HR = 0.89) advantage over 400 mg dose ($p = 0.04$) in progression-free survival (PFS), but no difference in overall survival (OS) (HR = 1.00) ($p = 0.97$). The 400 mg is thus the preferred dose for the treatment of GISTs, whereas the 800 mg daily dose was indicated in patients with exon 9 mutations in the kit gene or disease progression.[6] Subsequent trials have concluded that imatinib therapy can be used till progression of disease or development of intolerance.[7] Primary resistance to imatinib therapy is present in 10–15% of tumours, whereas acquired resistance develops in previously responsive tumours after a period of 18–24 months.[8] This is the rationale for combining surgery with primary imatinib therapy when this is feasible.[9] Therefore,

surgery remains a valuable tool in the management of GIST, and this takes place in varying presentations of GIST. This study seeks to analyse the outcomes in the management of GIST where surgery and imatinib are the only available options and to examine outcomes in surgery for the differing clinical scenarios.

Methods

The study was conducted in the KwaZulu-Natal province, at a tertiary hospital, Inkosi Albert Luthuli Central Hospital (IALCH). This was a retrospective chart review of all consecutive patients treated at the hospital by the GI oncology multidisciplinary team (MDT) from 2005 to 2020. Patients were grouped according to the National Institute of Health (NIH) risk stratification.[10] Tumour rupture and spillage were also markers of high-risk disease. Time of follow-up from initiation of treatment to time of last visit (time to discharge for best supportive care or death) was noted. PFS was defined as the time of initiation of therapy to last visit.

R0 and R1 resections were classified as macroscopically tumour-free margins with R0 microscopically negative and R1 positive margins. R2 was macroscopically positive margins. Simple resections were defined as single organ resections and complex resections as multivisceral, metastatic resections or surgery for recurrent disease.

A minimum of 36 months of therapy with imatinib was administered according to the National Comprehensive Cancer Network (NCCN) consensus guidelines in the adjuvant setting.[11] In disease progression or failure to respond, the imatinib dose was increased from 400 mg to 800 mg daily.

The practice was to treat patients with locally advanced, recurrent or metastatic GIST at presentation with imatinib therapy for a period not exceeding 12 months, followed by surgery for complete excision of the tumour or for cytoreductive surgery if this was deemed feasible and appropriate by a MDT assessment. In intermediate or high-risk cases, a minimum of 36 months of adjuvant imatinib was used and therapy was maintained until there was disease progression, or severe side effects occurred.

It is not clear which patients benefit the most from surgery after imatinib therapy. It is with this in mind that we examined all patients subjected to surgery after imatinib and compared outcomes of these in relation to resection margins, metastatic disease, multivisceral resection and repeat surgical excision of remnant disease. Disease response was evaluated by the Choi criteria on computed tomography (CT) scan and positron emission tomography (PET) scan imaging (Table I).[12] Response to treatment was defined as complete response (CR) if there was disappearance of the target lesion(s) at CT and PET scan, partial response (PR) if there was a ≥ 10% decrease in tumour size or ≥ 15% decrease in tumour attenuation at CT, recurrent/ progressive disease (PD) if there was ≥ 10% increase in the sum of the longest diameter of the lesion(s), new or an increase in the size of the existing intra-tumoral nodules, whereas stable disease (SD) had none of the above findings on CT scan and PET scan.

Survival curves, PFS and OS estimates and standard errors were obtained by the Kaplan–Meier method. Continuous variables were presented as median and interquartile range and the Mann–Whitney U test analysed difference between median values.

Table I: CHOI criteria[12]

Choi criteria
1. Complete response
Disappearance of all target lesions
2. Partial response
≥ 10% decrease in tumour size at computed tomography (CT); or ≥ 15% decrease in tumour attenuation at computed tomography (CT); no new lesions
3. Progressive disease
≥ 10% increase in sum of longest diameters (SLD) of lesions; does not meet the criteria for partial response by virtue of tumour attenuation; new intra-tumoral nodules or an increase in the size of the existing intra-tumoral nodules
4. Stable disease
None of the above

Results

Sixty-two patients were available for review from 2005 to 2020. Six patients (10%) did not have surgery performed. Four had poor surgical risk, one declined surgery and one was referred to another centre for surgical management. Fifty-six patients were subjected to surgery, 15 at referring hospitals and 41 at this institution. There was a significant difference in the size of tumours treated with surgery alone and those with surgery and imatinib (p = 0.013) (Figure 1). There was no significant difference in size between those having adjuvant and neoadjuvant therapy (p = 0.498). However, eight of 15 patients who had their primary surgery at the referring hospital were candidates for neoadjuvant therapy. Thirty-seven (54%) of the patients had follow-up periods that exceeded 2 years, 20 (29%) more than 5 years and 2 (3%) more than 10 years. The median age (range) was 58.5 (8–95) years. An eight-year-old patient who presented with a rectal tumour and was treated with an abdominoperineal resection is alive after 168 months. The median PFS and OS (IQR) was 24.0 (0–52.0) and 41.0 (15.0–74.0) months, respectively. Twelve (19%) and 19 (31%) of patients had not reached these median survivals at the time of analysis, respectively.

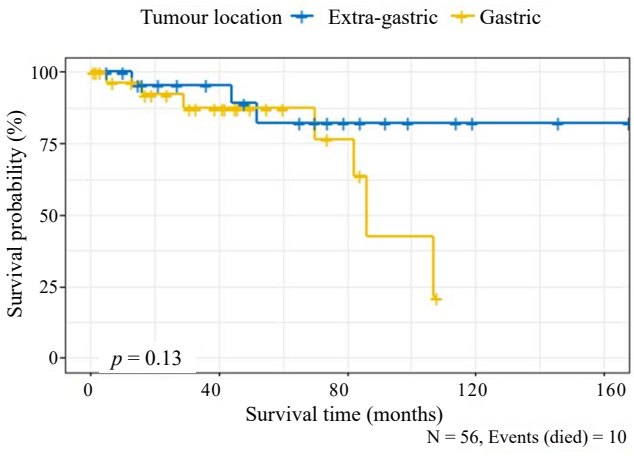

Figure 1: Tumour location and survival

Table II

Confounders	Surgery alone	Imatinib (n = 42)		Total
		Neoadjuvant	Adjuvant	
	20	21	27	56
Site				
Gastric	12	9	18	39
Extra-gastric	8	5	9	22
Size (median ± SD)	5 ± 8	12 ± 8	10 ± 10	7 ± 10
Resection margins				
R0	18	12	20	49
R1	2	2	6	8
R2	1	1	5	6
Liver resection	1	3	5	6
Multivisceral	0	3	3	5
CD34	11	14	24	16
CD117	14	22	28	18
DOG1	2	4	7	2
Treatment response				
CR	11	2	7	20
PR	N/A	11	6	17
Stable	N/A	1	4	4
Therapy stopped	N/A	0	4	4
Mortality	4	2	3	15

Most of the tumours were in the stomach and over 40% were high risk (Table II). Immunohistochemical assessment revealed that 55 (88.7%), 46 (74%) and 13 (20.9%) were positive for CD117, CD34 and DOG1 markers, respectively. Twenty-seven (44%), 22 (35%) and 13 (21%) were assessed as localised, locally advanced, and metastatic at presentation, respectively. Four metastases were to the lung, six to the liver and one peritoneal. One patient with neurofibromatosis, with a resected gastric GIST (CD117/34 positive), had recurrence after 1 year.

Thirty-nine (70%) of the patients who had surgery were treated with imatinib, with 21 treated in a neoadjuvant setting. Seventeen (27%) patients did not receive imatinib. In this group thirteen (65%) had very low- and low-risk disease and were referred for postoperative surveillance for recurrence. Two were referred to another oncology department in the province and the other two were repatriated to another province and to a neighbouring African country and thus lost to follow-up. Three patients died after surgery, one on day 8 and the other two four to five months after surgery from respiratory complications.

In patients undergoing surgery, surgical margins were R0, R1 and R2 in 41 (75%), eight (15%) and six (11%) respectively. There was an insignificant difference in the OS in these three groups (p = 0.24) (Figure 2). Six patients with liver metastases had resection of the primary tumour and the metastases. Four of the metastases were synchronous and two metachronous, and all had R0 resection margins for the primary disease and metastases. All six patients had imatinib prior to surgery and showed partial response of disease on CT scan and PET scan. All were alive at the

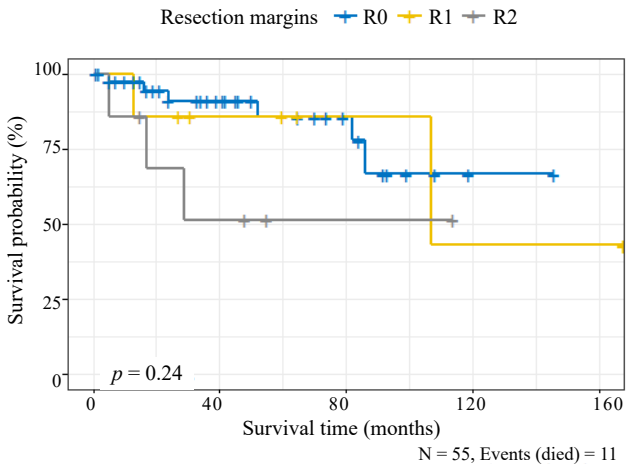

Figure 2: Resection margins and survival

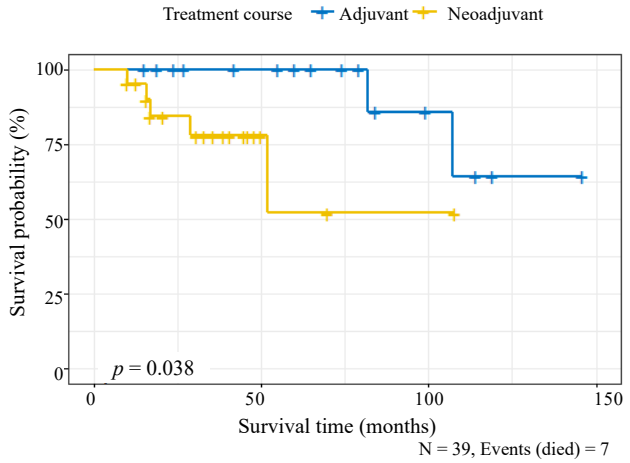

Figure 3: Imatinib therapy regimes and overall survival

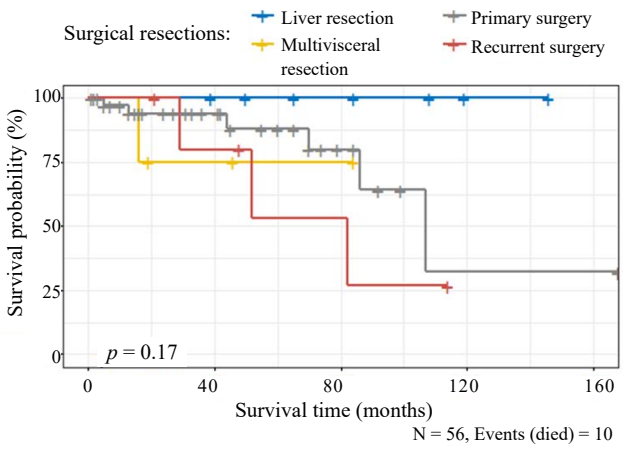

Figure 4: Extent of surgery

time of analysis. Two patients with a rectal tumour required abdominoperineal resection and one with an oesophageal tumour a limited oesophagectomy. Multivisceral resections included stomach, pancreas, and spleen in four patients (all R0), stomach and colon (R1), bladder and ileum (R1), and rectum and bladder (R2).

A single patient in the cohort received sunitinib after a partial gastrectomy in July 2007. The patient had exon 9 and 13 mutations. He received adjuvant imatinib for 44 months and had a left hepatectomy for recurrence in May 2013. He secured sunitinib privately and was without recurrence

in September 2019 for a survival period of greater than 11 years.

The median PFS and OS of patients receiving neoadjuvant and adjuvant therapy was 28.0 (9.00–56.3) and 34.0 (8.00–42.0), versus 34.5 (16.8–46.5) and 74.0 (45.3–95.3) months respectively (p = 0.038) (Figure 3). The proportion of gastric tumours with high risk (45%) was insignificantly higher than the proportion of extra-gastric tumours (34%) (p = 0.36). The median PFS (months) and OS (months) for the extra-gastric and gastric tumours was 30 (0–67.0) and 17 (2.00–43.0) (p = 0.354) versus 52.0 (16.0–84.0) and 33.0 (13.0–60.0) months respectively (p = 0.056).

For liver resection and multivisceral resections, the PFS and OS were 80 (50.5–92.3) and 96 (58.5–116), and 28.5 (5.75–49.8) and 32.5 (17.5–60.3) respectively (p = 0.008). For repeat surgery, OS was 50.0 (33.8–74.5) months (Figure 4).

Discussion

Most patients with GIST have a median age above 60, with a wide range of up to 10–92 years,[5] similar to the median age in this study. When compared to other studies the organ distribution was also similar, showing a higher predilection for the stomach. The expression of CD34 is similar to the other studies, but the prevalence of CD117 and DOG1 was lower in our study and requires further investigation.[13]

Contrary to other studies where non-gastric GISTs have been demonstrated to have poorer prognosis, non-gastric GISTs in this study did not convey a poorer prognosis as expected but this finding did not reach any statistical significance.[14] This is partly explained by gastric tumours having an insignificantly higher proportion of patients presenting with high-risk tumours.

The median OS of patients with locally advanced disease who underwent multivisceral resection, and those with metastatic disease are comparable to other studies. In a previous report, after a follow-up of 71 months, the median PFS was 24 months and the OS 57 months in patients with advanced GIST (metastatic and locally advanced).[15] In the current study, the OS for multivisceral surgery was poorer than that for metastatic resections at 32.5 (17.5–60.3) and 96.0 (58.5–116) months, respectively.

Patients with neoadjuvant therapy had poorer survival figures than those with adjuvant therapy. This is due to the initial group having more advanced disease at presentation and thus necessitating the need for neoadjuvant therapy. However, eight (38%) patients in the adjuvant group were candidates for neoadjuvant therapy but were not discussed by an MDT prior to surgery. Similar to our findings of survival of R2 resections, there have been reports, mainly case reports, of cytoreductive surgery resulting in prolonged survival.[16]

There are few prospective randomised controlled trials (RCTs) addressing the issue of the benefit of metastatectomy or R1 and R2 resection. There is conflicting evidence about the management of metastases to the liver. The controversy is whether these should be managed with a combination of surgery and tyrosine kinase inhibitors (TKIs), or TKIs only. In support of the benefit of surgery, some reports demonstrated that the 1- and 3-year survival was better in patients who had surgery at 100% and 89% versus 85% and 60% for those who received TKI only.[17] In another study, however, PFS after a median follow-up of 23 months (range 15–34) was insignificantly different between the surgery group (n = 19) and imatinib alone (n = 22) at 88.4% and 57.7% respectively (p = 0.89).[17] In a retrospective study of 239 patients, R0 and R1 resections had survival benefit as opposed to R2 which showed no survival benefit.[18] Whilst our findings demonstrate similar survival between R0, R1, and R2 resection margins when cytoreductive surgery was combined with imatinib therapy, these outcomes were not statistically significant and may be skewed due to the small sample size and a type 2 error. In a review, the benefits of cytoreductive surgery were more pronounced in patients with imatinib responsive GISTs.[19]

The outcomes of liver resection in this study were similar to those reported by Bauer et al., where median OS could not be obtained for individuals who had single organ metastasis involving the liver, 7 years for intra-peritoneal spread and 3.7 years in both liver and intra-peritoneal metastatic disease.[18] They identified female gender, short interval of imatinib to resection status (R0/R1), non-progressive disease at the time of surgery and liver site as positive prognostic factors.

Resistance to imatinib develops at a median time of 2 years from treatment onset and affects most patients after 4 years.[15,20] However, in patients who continued imatinib therapy beyond three years (56/147, 38%), after a median follow-up time of 9.4 years, 26 (17.7%) remained on imatinib therapy since study entry.[21] The estimated PFS rate at 9 years for all 147 patients was 14%. This was similar for patients with CR or SD. The estimated 9-year OS rate for all patients was 35–38% for those with CR/PR; 49% for SD; 0% for PD. This has resulted in GIST clinical guidelines recommending that imatinib treatment for patients with advanced GIST be continued until tumour progression.[22] More targeted therapies are now available when resistance to imatinib develops.[23-27] These were evaluated on patients with advanced disease and not in a neoadjuvant or adjuvant setting. Their role in surgical candidates is yet to be elucidated.

Conclusion

The distribution of GIST in our population is similar to other studies. Although these are small numbers of patients with a possible type 2 error, there are some trends to be observed. Surgery with the use of imatinib results in survival benefit in patients with R0, R1, R2, liver metastases and multivisceral resections. More appropriate management decisions are better made in a setting of MDTs and more patients who are eligible to receive targeted therapy would get treatment, especially in the neoadjuvant setting.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required.

Ethical approval

Full ethical approval was obtained from BREC. (BREC Ref No.: BE278/19) Due to the retrospective nature of the study, Hospital and Provincial Department of Health approval was granted to obtain necessary data from medical records. (NHRD Ref: KZ_201906_004). Written informed consent was waived by the ethics committee because of the study was non-interventional and retrospective in nature.

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REFERENCES

1. Rubin BP, Heinrich MC. Genotyping and immunohistochemistry of gastrointestinal stromal tumors: an update. Semin Diagn Pathol. 2015;32(5):392-9. https://doi.org/10.1053/j.semdp.2015.02.017.
2. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomarkers Prev. 2015;24(1):298-302. https://doi.org/10.1158/1055-9965.EPI-14-1002
3. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumours: recurrence patterns and prognostic factors for survival. Ann Surg. 2000;231:51-57. https://doi.org/10.1097/00000658-200001000-00008.
4. Chiappa A, Zbar A, Innis M, et al. Prognostic factors affecting survival after surgical resection of gastrointestinal stromal tumours:a two-unit experience over 10 years. World J Surg Oncol. 2006;4:73. https://doi.org/10.1186/1477-7819-4-73.
5. Miettinen M, Wang Z-F, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol. 2009;33(9):1401-8. https://doi.org/10.1097/PAS.0b013e3181a90e1a.
6. Kang GH, Srivastava A, Kim YE, et al. DOG1 and PKC-theta are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors. Mod Pathol. 2011;24(6):866-75. https://doi.org/10.1038/modpathol.2011.11.
7. 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):1127-34. https://doi.org/10.1016/S0140-6736(04)17098-0.
8. Gastrointestinal Stromal Tumor Meta-Analysis Group. 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):1247-53. https://doi.org/10.1200/JCO.2009.24.2099.
9. Proudman D, Miller A, Nellesen D, et al. Financial implications of avapritinib for treatment of unresectable gastrointestinal stromal tumors in patients with a PDGFRA Exon 18 variant or after 3 previous therapies in a hypothetical us health plan. JAMA Netw Open. 2020;3(11):e2025866. https://doi.org/10.1001/jamanetworkopen.2020.25866.
10. O'Regan KN, Shinagare AB, Saboo SS, et al. Gastrointestinal stromal tumors (GIST): lesser known facts. Clin Imaging. 2013;37(5):821-9. https://doi.org/10.1016/j.clinimag.2013.04.005.
11. National Comprehensive Cancer Network. Gastrointestinal stromal tumours (GISTs) version 1.2021 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf.
12. Benjamin RS, Choi H, Macapinlac HA, et al. Response of gastrointestinal stromal tumors (GISTs) to imatinib by Choi criteria and response evaluation criteria in solid tumors (RECIST) as surrogates for survival and time to progression. J Clin Oncol. 2006;24 Suppl 18:9506. https://doi.org/10.1200/jco.2006.24.18_suppl.9506.
13. Miettinen M, Wang Z-F, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol. 2009;33(9):1401-8. https://doi.org/10.1097/PAS.0b013e3181a90e1a.
14. Qi Y, Zhao W, Wang Z, Li T, Meng X. Tumor sites and microscopic indicators are independent prognosis predictors of gastrointestinal stromal tumors. Tohoku J Exp Med. 2014;233(1):65-72. https://doi.org/10.1620/tjem.233.65.
15. Blanke CD, Demetri GD, Von Mehren M, et al. Long-term results from a randomised phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. 2008;26(4):620-5. https://doi.org/10.1200/JCO.2007.13.4403.
16. Choi WH, Kim S, Hyung WJ, et al. Long-surviving patients with recurrent GIST after receiving cytoreductive surgery with imatinib therapy. Yonsei Med J. 2009;50(3):437-40. https://doi.org/10.3349/ymj.2009.50.3.437.
17. Xia L, Zhang MM, Ji L, Li X, Wu XT. Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. Surg Today. 2010;40(10):936-42. https://doi.org/10.1007/s00595-009-4171-x.
18. Bauer S, Rutkowski P, Hohenberger P, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib: analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol. 2014;40(4):412-9. https://doi.org/10.1016/j.ejso.2013.12.020.
19. Kikuchi H, Hiramatsu Y, Kamiya K, et al. Surgery for metastatic gastrointestinal stromal tumor: to whom and how to? Transl Gastroenterol Hepatol. 2018;3:14. https://doi.org/10.21037/tgh.2018.02.02.
20. Wardelmann E, Merkelbach-Bruse S, Pauls K, et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res. 2006;12(6):1743-9. https://doi.org/10.1158/1078-0432.CCR-05-1211.
21. Von Mehren M, Heinrich MC, Joensuu H, et al. Follow-up results after 9 years (yrs) of the ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST). J Clin Oncol. 2011;29(Suppl 15):10016. https://doi.org/10.1200/jco.2011.29.15_suppl.10016.
22. Casali PG, Blay JY, Experts ECECPo. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v98-102. https://doi.org/10.1093/annonc/mdq208.
23. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomised phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol. 2007;25(9):1107-13. https://doi.org/10.1200/JCO.2006.09.0183.
24. Waddell T, Cunningham D. Evaluation of regorafenib in colorectal cancer and GIST. Lancet. 2013;381(9863):273-5. https://doi.org/10.1016/S0140-6736(12)62006-6.
25. Jakhetiya A, Garg PK, Prakash G, et al. Targeted therapy of gastrointestinal stromal tumours. World J Gastrointest Surg. 2016;8(5):345-52. https://doi.org/10.4240/wjgs.v8.i5.345.
26. Demetri GD, Van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal

stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38. https://doi.org/10.1016/S0140-6736(06)69446-4.
27. Demetri GD, Reichardt P, Kang Y-K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID) - an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302. https://doi.org/10.1016/S0140-6736(12)61857-1.