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Quality of treatment and surgical approach for rectal gastrointestinal stromal tumour (GIST) in a large European cohort

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ABSTRACT

Background: Rectal gastrointestinal stromal tumours (GISTs) are rare tumours. Variability in the management may influence outcome, but there is a lack of understanding regarding contemporary variance in care. A multicenter, international, retrospective cohort study was performed to elucidate characteristics and outcomes of rectal GIST in European practice, with particular reference to surgical approach.
Methods: All rectal GIST patients diagnosed between 2009 and 2018 were identified from five European databases. Recurrence free survival (RFS) and overall survival (OS) were estimated using Kaplan-Meier method. Possible confounders were identified using Cox regression analyses.
Results: From 210 patients, 155 patients had surgery. The three main types of surgery were local tumour resection (LTR, n = 46), low anterior resection (LAR, n = 31) and abdomino-perineal resection (APR, n = 32). Most patients received neoadjuvant (65%) and/or adjuvant imatinib therapy (66%). Local recurrence rate after surgery was 15% and overall recurrence rate 28%. No significant differences were found in terms of RFS nor OS between LTR, LAR and APR. However, locally resected tumours were smaller, while LAR and APR patients more often received perioperative imatinib. General hospitals treated smaller GISTs, offered imatinib less frequently, and had a higher tumour rupture rate. In the

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multivariate analysis in the group having LTR, APR or LAR, the only significant prognostic factor for local recurrence was higher age (HR 1.06, CI 1.00–1.12, p = 0.048).

Conclusions: In European clinical practice for rectal GIST, LTR, LAR and APR have comparable local control. Multimodal approach is higher and tumour rupture less frequent in specialist centres compared to general hospitals.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are rare tumours arising from the mesenchymal tissue in the gastrointestinal tract with an estimated incidence of 10–15 per million per year[1]. Approximately 5% of the GISTs occur in the rectum[2–5]. Variability in the management of this rare tumour may influence outcome, but there is a lack of understanding regarding contemporary variance in care. Due to the rarity of GIST, a multidisciplinary approach with the involvement of centres with relevant expertise has been recognized as an important factor[6]. There is however limited evidence-based data regarding the treatment of rectal GIST. Most published studies are either single centre experiences with limited number of patients[7–12] or series lacking detailed data about important prognostic factors[13,14], which makes it difficult to interpret the data and limits the clinical application.

Furthermore, since GISTs located in the rectum has been described as an adverse prognostic factor[15], the European Society of Medical Oncology (ESMO) guidelines state that surgical resection should be considered in all rectal GIST patients, irrespectively of tumour size[6]. Furthermore, MRI is advised as primary imaging modality. However, specific surgical strategies are not discussed within ESMO guidelines. Consideration of the surgical approach, is important due to the technically challenging nature of rectal GIST, relating to the precise site of origin in the rectum, its relation to the sphincter complex, the risk of tumour rupture and positive margins, and the relationship to vital structures in the pelvic cavity. The decision about the approach and extent of surgery is therefore crucial for achieving histologically negative margins and at the same time it should be balanced according both to oncological risk and functional morbidity. Other considerations in this group of patients are related to the mode of biopsy, the influence and timing of neoadjuvant treatment on mode of surgery and oncological outcomes, and whether there is benefit in being managed in a high-volume specialist centre.

To address some of these questions, we present a multicentre, international retrospective study including patients with rectal GIST from five European countries, which represents one of the largest series in rectal GIST. The primary aim of this study is to elucidate the characteristics of rectal GIST and outcome of different treatment modalities in contemporary European practice.

2. Methods

2.1. Study design and patient selection

This is a retrospective, multicenter, international cohort study. We adhered to the STROBE guidelines for cohort studies. Data from five different GIST databases were combined to achieve an adequate sample size. All patients diagnosed with rectal GIST between January 2009 and January 2018 were selected to prevent any type of selection bias. Participating countries were the Netherlands (Dutch GIST consortium, sites: UMC Groningen, Netherlands Cancer Institute, Leiden UMC, Erasmus MC, Radboud MC), Italy (site: Fondazione IRCSS Istituto Nazionale dei Tumori Milano), France (French Sarcoma Group, sites: NetSarc centres), UK (site: the Royal Marsden Hospital) and Poland (site: Maria Sklodowska-Curie National Research Institute of Oncology). Patients were excluded from the analysis when essential information was missing, being gender and whether patients underwent surgery.

2.2. Main outcome measures

The primary endpoint was to describe the outcomes of rectal GIST in European practice, in terms of local recurrence rate, recurrence free survival (RFS) and disease specific survival (DSS). Secondary descriptive endpoints were tumour characteristics (i.e. size, mitotic count, mutational status, baseline distance to anal verge), the impact of neoadjuvant and adjuvant imatinib therapy (i.e. time to maximal tumour reduction, change in size and mitotic count, percentage of post-treatment viable cells), number of patients with radiotherapy and surgery characteristics (i.e. type of surgery, severe complications classified by at least grade 3b according to Clavien-Dindo classification, margins, peroperative tumour rupture).

2.3. Surgical procedures

Local tumour resection (LTR) includes transanal excision, transanal endoscopic microsurgery and transperineal approach for resection of the anal canal. Two other common surgical procedures were low anterior resection (LAR) and abdomino-perineal resection (APR).

2.4. Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 25. Time to maximum reduction of tumour size on neoadjuvant imatinib treatment was calculated from start date until the date of the maximum achieved radiological reduction. Survival estimates were obtained using the Kaplan-Meier method and compared by log-rank test. RFS was calculated from date of surgery to date of recurrence or date of last follow-up. DSS was calculated from the date of diagnosis to date of death or date of last follow-up. Potential confounders were identified by using univariate Cox regression analysis. Only confounders with a p-value below 0.3 were subsequently included in the multivariate analysis. All tests were two-sided and a p-value of <0.05 was considered significant. In the group with the three main types of surgery, multiple imputation (Predictive Mean Matching, 20 times, 50 iterations) was performed in SPSS for missing values of likely confounders.

3. Results

3.1. Patient characteristics

In total, 231 patients with rectal GIST were identified from the databases. After exclusion of 21 patients due missing essential information, 210 patients were ultimately included: 48 patients from

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the Netherlands, 35 from Italy, 22 from the UK, 36 from Poland and 69 from France.

Median age in these 210 patients was 61 years with 63% being male (Table A1). Median tumour size at diagnosis was 65 mm and median baseline distance to anal verge 34 mm. Three most common reported symptoms at diagnosis were rectal mass, rectal bleeding and change in bowel habit. Mutation status was known for 156 patients (74%). Most of the GISTs were *KIT* exon 11 mutated (71%), but also mutations in *KIT* exon 9 (14%), *KIT* exon 13 (3%), *PDGFR* (n = 1) and *KIT/PDGFR* wildtype (12%) were reported. Mitotic rate at baseline was low (≤5/50 HPF) in 59% and high (>5/50 HPF) in 41% of the patients.

In this cohort, 55 patients did not undergo surgery (Fig. A1). The main reason for this was metastatic disease, other reasons were unfitness for surgery, patients declining surgery and ongoing response on systemic treatment. From the surgeries, LTR was most often performed, followed by APR and LAR.

3.2. Main types of surgery

The group with the three main types of surgeries (LTR, LAR and APR) consists of 109 patients (Table A2). None of these patients had metastatic disease at diagnosis. Median age in this group was 61 years and 70% were male. Median baseline tumour size was 61 mm and median distance to the anal verge 35 mm. In one patient, the tumour extended into the sphincter and in 4 patients it was ≤1 cm from the sphincter. Most GISTs were *KIT* exon 11 mutated (74%). Comparing the three groups of surgery, smaller tumours more often had LTR. No significant differences were found in baseline mitotic rate, peroperative tumour rupture and resection margins. The severe complication rate was low (4.4%). Patients with a LAR or APR received neoadjuvant imatinib therapy more frequently compared to the LTR group (77% or 91% vs. 54% resp.), but this difference was not noticed in the adjuvant treated group (86% or 61% vs. 61% resp., p = 0.062). When comparing LAR with APR separately, patients with a LAR received adjuvant imatinib more often than patients having an APR (86% vs. 61%). No other differences were found in characteristics between patients with a LAR and APR.

3.3. Location of surgery: general hospital versus specialist centre

For 140 patients that had surgery (90%) the type of hospital was specified. Fifty-one (36%) operations were performed in a general hospital not specialized in GIST surgery. These operations were mainly LTRs and baseline tumour size was smaller (median 44 mm vs. median 67 mm, p = 0.002). Patients that had surgery in general hospitals were less often treated with neoadjuvant and adjuvant imatinib (13% vs. 96% (p < 0.001) and 51% vs. 72% (p = 0.026) resp.). No difference was found in resection margins (p = 0.131), but peroperative tumour rupture was more often reported in general hospitals compared to specialized centres (37% vs. 5%, p < 0.001). Local RFS was significantly shorter for all patients with peroperative tumour rupture (n = 17) in univariate KM analysis (p < 0.001, median not reached), but this effect was lost in multivariate Cox regression analysis. Furthermore, no statistically significant difference was detected for local RFS between patients that underwent surgery in a general hospital or specialist centre (p = 0.240, median not reached).

3.4. (Neo)adjuvant treatment

In the surgery cohort, most of the patients received neoadjuvant (65%) and/or adjuvant therapy (66%). Neoadjuvant therapy was imatinib 400 mg QD in 91% of the cases, and few received imatinib 800 mg QD (n = 7, mostly *KIT* exon 9 mutated) or masitinib or sunitinib if there was severe imatinib toxicity (n = 2 and n = 1 resp.). Median time on neoadjuvant treatment was 10 months (range 1–102), whereas the time to maximum tumour reduction, reviewed retrospectively and available for only 45% of patients, was 6 months (median, range 2–38). Patients treated with neoadjuvant imatinib had a median size reduction of 33% (range −100 to 20%, available for 86% of the patients) and a decrease in mitotic count of 2.5 (median, range −39 to 11, only available for 36% of the patients). The median percentage of viable cells after neoadjuvant therapy was 30% (0–100, available for 51% of the patients). Median time on adjuvant imatinib treatment was 25 months (range 0–112). In the whole cohort at least 12 patients received radiotherapy. Four patients were treated with radiotherapy adjuvant because of high risk features and, remarkably, only one of them had a recurrence.

3.5. Outcome in general

Median follow-up time after surgery was 28 months (range 0–115). During this follow-up time 43 patients had a recurrence (recurrence rate 28%): 17 patients a local recurrence (recurrence rate 11%), 19 patients had distant recurrent disease only (recurrence rate 12%) and 7 patients had simultaneously local and distant recurrent disease (recurrence rate 5%). Median all RFS was 75 months (95% confidence interval (CI) of 64–85 months). Median local RFS was not reached. Overall 12 patients died from which 10 died of disease (5%), but most of them did not have surgery: only 3 patients that underwent surgery died of disease (2%). There was no difference in DSS (p = 0.644) comparing the three main types of surgery.

3.6. Prognostic factors for a local recurrence within the group with three main surgeries

Using the Kaplan Meier method, local RFS did not differ between the three main surgeries (Fig. A2). No difference in local RFS was found comparing the country of surgery (p = 0.348). Furthermore, local RFS was not significantly longer after adjuvant imatinib (p = 0.848) nor neoadjuvant imatinib (p = 0.186). No difference in local RFS was found comparing high risk rectal GIST (size >5 cm, mitotic count >5 and/or peroperative tumour rupture) with low risk rectal GIST (p = 0.283).

Cases with missing data were automatically excluded from the Cox regression analysis. To make the results more reliable, multiple imputation of the missing data was done for the expected possible confounders within the group of three main surgeries (percentage missing data: baseline mitotic rate 42%, distance to anal verge 25%, peroperative tumour rupture 21%, severe complications 17% and mutation status 16%). After multiple imputation, Cox regression analysis was performed (Table A3). Using the p-value threshold of 0.3, older age, larger baseline tumour size, closer to anal verge, positive resection margin, peroperative tumour rupture and no neoadjuvant imatinib were associated with worse local RFS on univariate Cox regression analysis. In multivariate analysis, using a p-value threshold of 0.05, the only significant prognostic factor for local recurrence was older age (HR 1.057, CI 1.000–1.116, p = 0.048).

4. Discussion

In this retrospective cohort study, the characteristics of rectal GIST in European practice were investigated. The average rectal GIST patient in this series is 61 years old and male (63%), presenting most commonly with a rectal mass, rectal bleeding or a change in bowel habits. The vast majority has a resection of the primary tumour, being most frequently a LTR, LAR or APR. The recurrence rate after surgery was high, despite the majority of patients having

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perioperative treatment with imatinib. Smaller tumours were most likely treated by LTR, while LAR and APR patients received more often perioperative imatinib therapy. LTR, LAR and APR appear to have comparable oncological outcome.

Several European studies relating to rectal GIST have been published [7–10], all focusing on differences in outcome after surgery with and without neoadjuvant imatinib, but these studies suffer from small sample sizes and may not reflect contemporary practice. Two recent studies were performed with a larger sample size, but are limited by lack of detailed data about important prognostic factors, tumour size prior to pre-operative therapy and recurrence rate [14,16]. Our cohort has the benefit of having a larger sample size, representing multiple institutions, with a wide range of variables that may help inform practice.

Contrary to expectations, in our cohort, tumour rupture and negative resection margins did not appear to influence the risk for recurrence in multivariate analysis. A possible explanation could be a protective effect of perioperative imatinib, but this did not appear to reduce the risk for local recurrence in multivariate analyses either. That may be related both to selection bias in treating patients at higher risk with imatinib and to the relatively low number of events.

The median time of maximum tumour reduction on neoadjuvant imatinib in our series was 6 months. This duration is in line with the time to maximum tumour reduction of 6.9 months found by Wang et al. in 17 rectal GIST patients[17]. Despite the dogma that optimal neoadjuvant imatinib therapy takes longer in rectal GIST patients, the duration of treatment to maximal tumour regression seems comparable to other GIST locations[18,19]. Furthermore, the range of optimal response time is wide and frequent scans to evaluate response should be scheduled.

In this cohort, twelve patients had radiotherapy. Due to the overall good response rates to imatinib, reliable data about the influence of radiotherapy is scarce[6]. In recent years however, several studies were performed regarding radiotherapy in GIST. Joensuu et al. investigated radiotherapy in 25 metastatic GIST patients, whereof 19 patients were concomitantly treated with tyrosine kinase inhibitors. Responses to radiotherapy were infrequent (8%), but most patients had durable stabilization (80%) despite confounding from TKI treatment is likely[20]. Some other series show promising results in specific scenarios, but more studies are needed to determine the specific influence of radiotherapy on oncological outcome[21–23]. However, radiotherapy can be considered among possible therapeutic options in patients who do not want surgery and wish to stop or are progressive on TKIs.

Consideration should be given to the type of institution initial surgery was performed, and if there is any potential influence on outcomes. We observed that despite the smaller tumour size in general hospitals, the frequency of tumour rupture was higher in general hospitals compared to specialist centres. This suggests that the quality of surgery was superior in specialist centres: despite smaller cancers and less extensive surgery, there was a higher rate of tumour rupture in general hospitals. Moreover, patients had lower chance to be offered multimodal treatment in general hospitals. Nevertheless, the oncological outcome was not different in general hospitals, which might be explained by selection bias where the high risk tumours are referred to specialized centres. These findings highlight the importance of management of rectal GISTs in specialist centres. The overall rarity of rectal GIST determines that they are very unfamiliar in routine clinical care. Management is frequently complex and pathways of care are complicated, which can be overcome by specialized multidisciplinary GIST care. Moreover, another advantage of centralized care is that more patients can be included in studies which will ultimately ensure improved care.

Of interest was that a substantial proportion of patients declined surgery when indicated. Declining end stomas and concerns regarding and the impact of surgery on quality of life were identified as the most common underlying motivations. This demonstrates the importance of shared decision making with patients and personalized surgery for patients with rectal GIST, in particular with the availability of alternative treatments to surgical resection.

The ESMO guideline recommends MRI as pre-operative imaging in rectal GIST. However, when collecting the data, we noticed that in the Netherlands quite often CT scans were done instead, probably due to limited capacity. In contrast, standard MRI scanning is done in the UK. Another interesting observation was that, additionally to MRI scanning, an examination under anesthesia including rigid sigmoidoscope digital rectal examination is performed pre-operatively in the RMH for optimal surgical planning. It would be interesting to determine the influence of these different ways of pre-operative tumour assessment on oncological outcome and choice of surgical approach in future research.

The main limitation of our study is the relatively short follow-up time compared to the median RFS (28 months vs. 75 months). The number of events is therefore low and definite conclusions can only be drawn after analysis of data with longer follow-up. Another problem is the amount of missing data in certain variables, which was addressed by using imputation. Furthermore, it would have been informative to ascertain what proportion of patients initially thought to require an APR, but ultimately had a sphincter sparing procedure after neoadjuvant treatment with imatinib. Nevertheless, this is the largest cohort of European rectal GIST patients to date, and one of the largest in the literature, and it is illustrative to combine all available data on such a rare tumour from countries that all manage patients according to the ESMO guideline.

5. Conclusions

This study represents a large cohort of surgically treated rectal GIST patients in Europe. In European clinical practice, smaller tumours are most likely treated by LTR, while the larger tumours are preferentially treated with LAR and APR and patients receive more often perioperative imatinib therapy. LTR, LAR and APR have comparable oncological outcome. Quality of treatment (multimodal approach, less peroperative tumour rupture) appears to be superior in specialist centres and referral of rectal GIST to specialist centres is therefore recommended.

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Declaration of competing interest

P. Rutkowski has received honoraria for lectures and Advisory Board from Novartis, Pfizer and Blueprint Medicines. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

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Table A1
Patient and tumour characteristics whole cohort of GIST patients.

Characteristic	No.	%
	210	100
Gender		
Male	132	63
Female	78	37
Age (median, range)	61 (18–91)	
Tumour size at diagnosis in mm (median, range)	65 (3–250)	
Distance to anal verge in mm (median, range)	34 (0–200)	
Most important symptom at diagnosis		
Rectal bleeding	27	13
Change in bowel habits	25	12
Rectal mass	22	11
Pain	16	8
Urinary tract problems	9	4
Incidental finding	9	4
Screening program	2	1
Vaginal bleeding	2	1
Not specified	22	11
Mutation status		
KIT exon 11	110	53
KIT exon 9	21	10
Wildtype (*KIT*/*PDGFR*)	19	9
KIT exon 13	5	2
PDGFR	1	1
Mitotic rate at baseline		
Low (≤5/50 HPF)	63	59
High (>5//50 HPF)	43	41
Surgery yes/no		
Yes	155	74
No	55	26

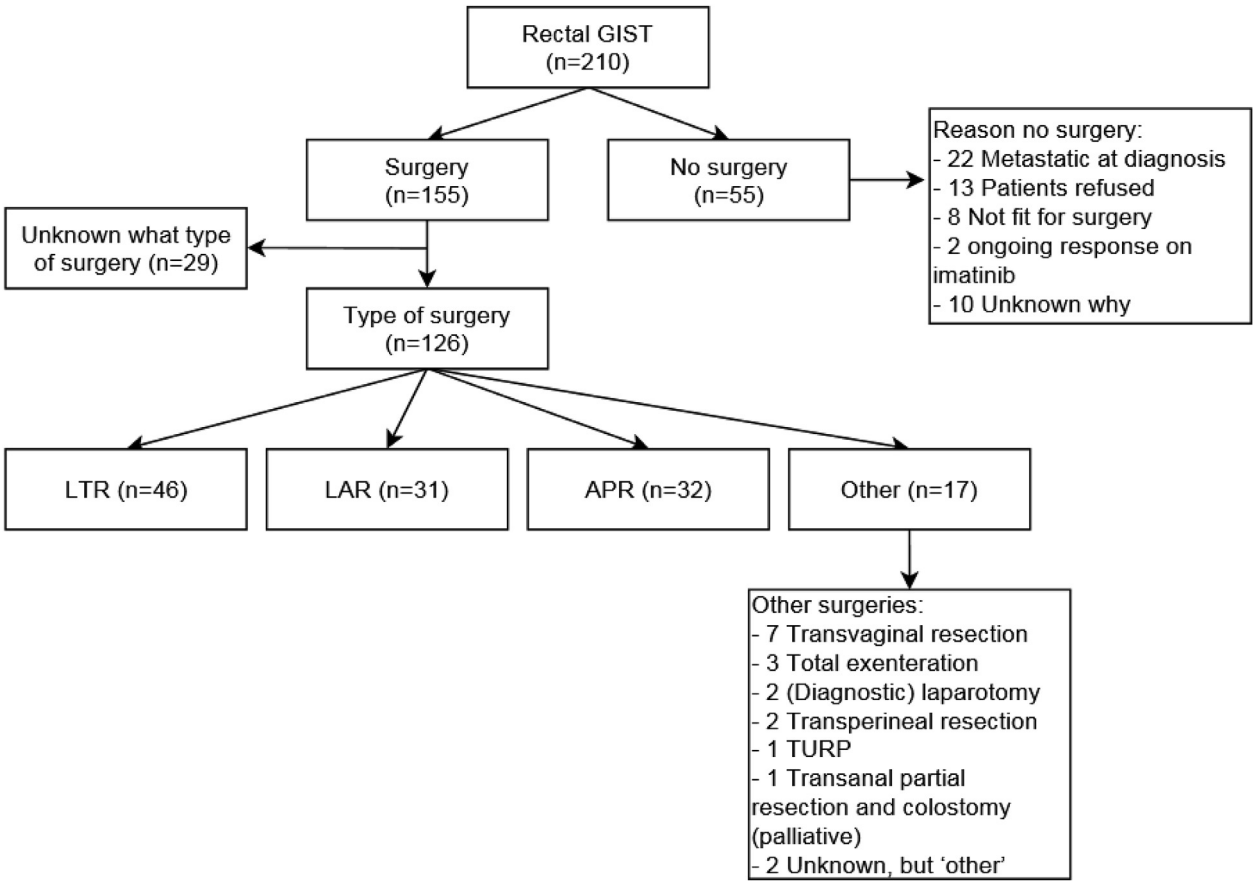

Fig. A1. Flowchart of rectal GIST patients.

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Table A2
Characteristics of rectal GIST patients with three main types of surgery (n = 109).

	No. (%)	LTR	LAR	APR	p-value
Number of patients	109	46	31	32	
Age (median, range)	61 (27–83)	61 (40–82)	62 (38–83)	61 (27–81)	0.942[A]
Gender					0.808[B]
Male	76 (70)	31	23	22	
Female	33 (30)	15	8	10	
Baseline size in mm (median, range)	61 (14–250)	50 (14–135)	70 (20–190)	82 (37–250)	<0.001[A]*
Baseline distance to anal verge in mm (median, range)	35 (0–80)	40 (10–80)	30 (19–60)	30 (0–80)	0.083[A]*
Mutation					0.533[B]
KIT exon 11	68 (74)	30	19	19	
KIT exon 9	14 (17)	3	5	6	
KIT exon 13	5 (5)	2	1	2	
Wildtype	5 (5)	1	3	1	
Baseline mitotic rate					0.246[B]
Low (≤5/50 HPF)	36 (57)	16	7	13	
High (>5//50 HPF)	27 (43)	11	10	6	
Type of hospital					0,001[B]*
Sarcoma centre	75 (69)	23	23	29	
General hospital	34 (31)	23	8	3	
Resection margin					0.438[B]
R0	67 (62)	26	18	23	
R1	31 (29)	14	11	6	
R2	10 (9)	6	2	2	
Peroperative tumour rupture					0.351[B]
No	73 (85)	27	20	26	
Yes	13 (15)	6	5	2	
Severe complications (>3a Clavien Dindo)					0,015[B]*
No	86 (96)	33	27	26	
Yes	4 (4)	0	0	4	
Stoma					<0.001[B]*
No	35 (32)	30	5	0	
Yes, protective stoma	42 (39)	16	26	0	
Yes, definite stoma	32 (29)	0	0	32	
Time to closure of protective stoma (median, weeks)	23 (5–120)	27 (11–73)	15 (5–120)	NA	0.085[C]
Imatinib neoadjuvant					
No	31 (28)	21	7	3	0,002[B]*
Yes	78 (72)	25	24	29	
Imatinib adjuvant					0.062[B]
No	33 (32)	17	4	12	
Yes	70 (68)	27	24	19	

*p < 0.05 is considered significant.
[A]Kruskal-wallis test.
[B]Chi square test.
[C]Mann Whitney *U* test.

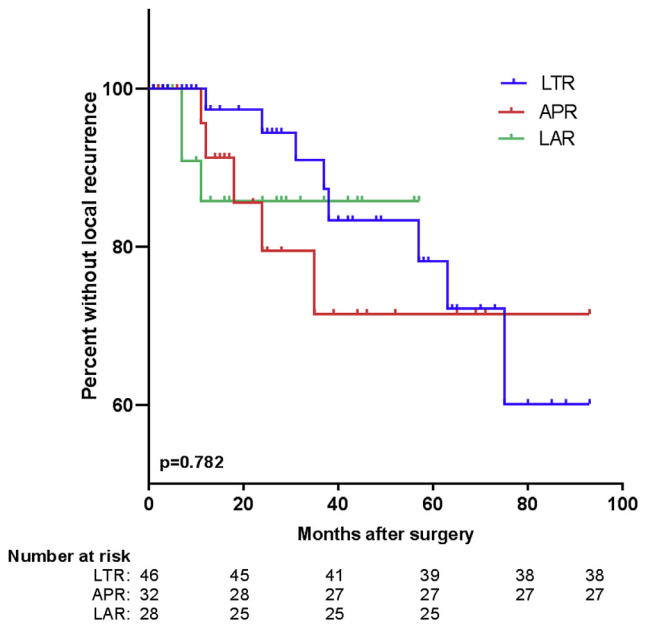

Fig. A2. Local recurrence free survival for three main groups of surgery.

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Table A3
Cox regression local recurrence free survival in rectal GIST patient with three main types of surgery LTR, LAR and APR, n = 109) after multiple imputation of missing data.

	Univariate analysis			Multivariate analysis		
	HR[a]	95% CI[b]	p-value	HR[a]	95% CI[b]	P-value
Gender						
Male	Reference					
Female	1.420	0.525–3.840	0.490			
Age	1.060	1009–1113	0.020*	1.057	1.000–1.116	0.048**
Size	1.008	0.995–1.020	0.234*	1.006	0.992–1.020	0.386
Baseline distance to anal verge	0.967	0.934–1.004	0.084*	0.976	0.934–1.021	0.288
Mutation						
KIT exon 11	Reference					
No *KIT* exon 11	0.681	0.196–2.368	0.546			
Baseline mitotic rate						
Low (≤5/50 HPF)	Reference					
High (>5//50 HPF)	1.663	0.392–7.051	0.487			
Type of surgery						
LTR	Reference					
LAR	1.300	0.331–5.114	0.707			
APR	1.478	0.478–4.571	0.498			
Resection margin						
R0	Reference					
R1	1.571	0.527–4.686	0.418	1.310	0.363–4.728	0.680
R2	3.492	0.880–13.860	0.075*	2.191	0.253–19.016	0.475
Peroperative tumour rupture						
No	Reference					
Yes	2.136	0.546–8.360	0.274*	1.597	0.213–11.977	0.645
Severe complications						
No	Reference					
Yes	0.864	0.003–246.108	0.960			
Stoma						
No	Reference					
Yes, protective stoma	0.767	0.223–2.638	0.674			
Yes, definite stoma	1.242	0.391–3.946	0.713			
Imatinib neoadjuvant						
Yes	Reference					
No	1.916	0.717–5.119	0.195*	1.562	0.496–4.915	0.446
Imatinib adjuvant						
Yes	Reference					
No	0.887	0.291–2.701	0.832			

*p < 0.3 in univariate and therefore included in multivariate analysis, **p < 0.05 is considered significant in multivariate analysis.
a: Hazard Ratio, b: Confidence Interval.

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