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Original Research

Local recurrence in primary localised resected gastrointestinal stromal tumours: A registry observational national cohort study including 912 patients

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Abstract ***Background and objectives:*** Previous literature showed a high risk of recurrence following surgical treatment in patients with gastrointestinal stromal tumours (GISTs). However, little is known about the patient- and treatment characteristics of local recurrences (LRs) in GIST patients. Therefore, this study aimed to better understand patterns of LR in surgically treated localised GIST and to describe treatment options based on our Dutch GIST Registry (DGR).

Methods: Data of primary surgically treated localised GIST between January 2009 until July 2021 were retrospectively retrieved from the DGR.

Results: Of 1452 patients registered in the DGR, 912 patients were included in this study. Only 3.8% (35/912) of patients developed LR, including 20 patients with LR only and 15 patients with simultaneous LR and distant metastases (DM). Median time to LR was 30 (interquartile range 8–53) months from date of surgery. Eleven percent (100/912) of patients

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developed only DM. A total of 2.3% (6/259) of patients treated with adjuvant treatment developed an LR during adjuvant therapy. Seventy percent of patients with LR only (14/20) were treated with surgery (85.7% R0), which was mostly combined with systemic treatment. ***Conclusions:*** Patients with primary surgically treated localised GIST have a limited risk of developing recurrence. Fifteen percent developed recurrence, of which one quarter developed an LR. Therefore, less intensified follow-up schedules could be considered, especially during treatment with adjuvant imatinib. In patients with LR only, potentially curative treatment strategies, including surgical (re-)resection, are often possible as treatment for LR.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are mesenchymal tumours originating from interstitial cells of Cajal arising predominantly in the gastrointestinal tract [1]. Primary tumours most often occur in the stomach (50–60%) and the small bowel (20–30%) [2,3]. Mutations in GIST are most often observed in the proto-oncogene receptor tyrosine kinase (*KIT*) gene and less frequently in the platelet-derived growth factor receptor α (*PDGFRA*). *KIT* exon 11 is the most common mutation, occurring in 70% of all GISTs [4].

Surgery is the first treatment option in primary localised GIST. However, 15–50% of the patients present with metastatic disease at diagnosis [1,5–8]. Since the implementation of tyrosine kinase inhibitors such as imatinib, the overall survival of metastatic GIST or locally advanced GIST dramatically increased [9–13].

For localised disease, after surgery, GISTs are usually classified as low-, intermediate-, and high-risk tumours according to the Miettinen's 2006 criteria to predict the risk of recurrence. The first accepted classification to define risk of aggressive behaviour in GISTs was the US National Institutes of Health Consensus Criteria (2001), which was based on tumour size and mitotic index [14]. The Miettinen's criteria, also known as the staging system of the American Joint Committee on Cancer, are based on tumour size, location and mitotic index [15]. In 2008, the Joensuu classification included tumour rupture as another important risk factor for a more individualised prediction of recurrence [16]. However, only 7% of all GIST show tumour rupture [17].

Since 2011, imatinib was officially implemented as adjuvant treatment for high-risk patients to reduce the risk of recurrence [18]. However, recurrence following surgery is still common [19]. Approximately half of the patients treated with curative intent develop recurrent disease. In 5–35% of patients, this is a local recurrence (LR) meaning recurrence at or near the primary tumour location [1,20–24]. Little is known about the patient- and treatment characteristics as well as the oncological outcome of LR in GIST patients.

Therefore, the main aim of this study is to better understand patterns of LR in surgically treated localised GIST and to describe treatment options based on our large series of data of Dutch GIST patients treated in GIST reference centres.

2. Methods

This multicenter study was approved by the local review boards of centres participating in the national database of patients with GIST in the Netherlands: the Dutch GIST Registry (DGR).

2.1. Study population

Patients of 18 years or older with primary GIST, surgically treated between January 2009 until July 2021, were selected from the DGR. Primary GIST was defined as local or locally advanced GIST, without distant metastases. The data were collected from the DGR database containing data of all adult GIST patients treated in one of the five Dutch GIST centres (UMC Groningen, LUMC Leiden, Erasmus MC Cancer Institute Rotterdam, RadboudUMC Nijmegen and the Netherlands Cancer Institute Amsterdam). Patients with metastases at entry, multiple primary tumours or patients that did not undergo a surgical resection were excluded.

2.2. Variables

Patient demographics and tumour characteristics including molecular pathology reports, treatment and follow-up data were collected. Locally advanced disease was defined as patients with non-metastatic disease and an indication for neo-adjuvant treatment. LR was defined as the first clinical, radiological (CT- and/or PET-scan and/or MRI-scan) or pathological manifestation of GIST within or contiguous to the previously treated tumour bed, three or more months after surgery with or without (neo-)adjuvant treatment. LR only was defined as LR without distant metastases (DM) at time of presentation of LR. Resection margins were defined as follows: R0, R1 and R2 corresponding to no residual tumour at the resection margin, microscopic residual tumour and intralesional macroscopic residual tumour, respectively. Tumour rupture was defined as

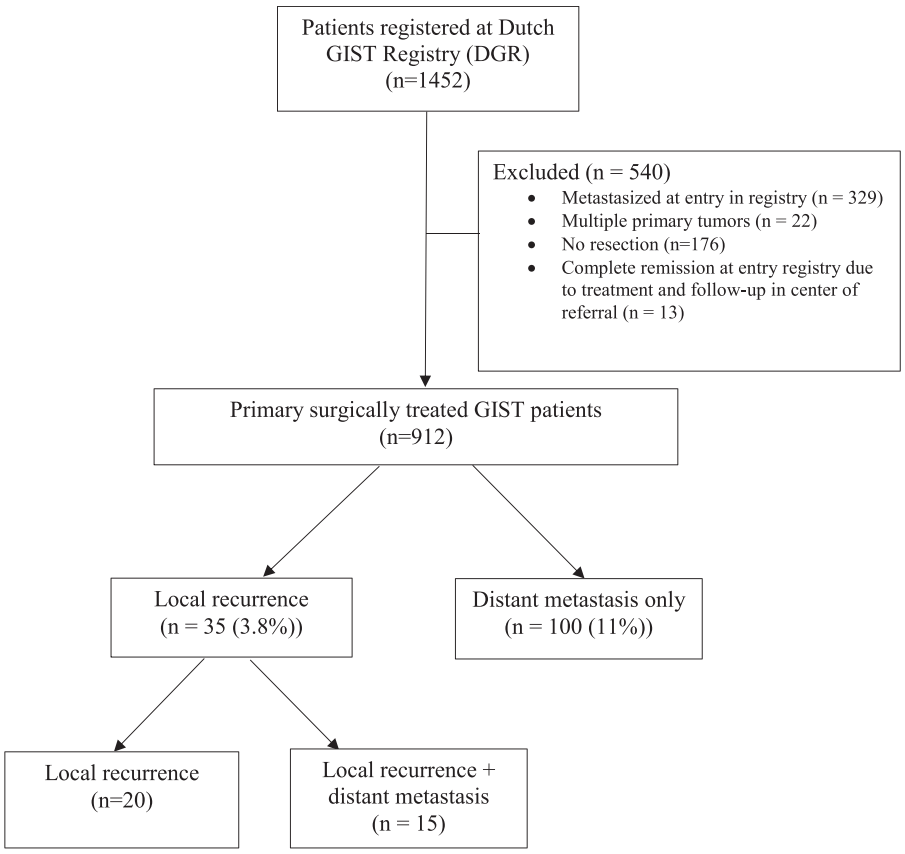

Fig. 1. Flowchart.

(microscopically) disrupted serosa, as described by an experienced pathologist, tumour spillage or gastrointestinal perforation at tumour site in the abdominal cavity. Mitotic rate was defined as high or low, that is, respectively, > 5 mitoses per 5 mm^2 or 50 High Power Fields (HPF) or ≤5 mitoses per 5 mm^2 or 50 HPF. Patients were classified into risk groups based on the Miettinen's criteria [15]. Mutational status was assessed by sequencing on formalin-fixed paraffin. Different hotspots of both KIT and PDGFRA genes were tested. In case of a wild-type GIST, there was no mutation found in the both KIT and PDGFRA genes. Time of follow-up (FU) was defined as date of surgery until date of last contact or dead.

2.3. Statistical analysis

Descriptive statistics were used to summarise patient- and tumour characteristics. For categorical or dichotomous variables, absolute numbers and percentages within each group were reported. For continuous variables, mean and standard deviation were reported in case of normally distributed data and median and interquartile range (IQR) were reported for non-normally distributed data. Baseline patient- and tumour characteristics were compared using the Chi-squared test or the Kruskal-Wallis test. All statistical analyses were performed using IBM SPSS Statistics 24.0 [25]. Values of $p < 0.05$ were considered as statistically significant.

3. Results

3.1. Study population

3.1.1. Baseline characteristics

From the 1452 patients registered in the DGR, a total of 912 GIST patients were included in this study cohort. Median FU in the entire study cohort was 30 months (IQR 8–62) from date of surgery with a range of 0–140 months. Five-hundred-forty patients were excluded due to diagnosis before 2009, metastases at time of registry in the DGR database, multiple primary tumours, no surgical treatment or surgical treatment and follow-up in centre of referral. Thirty-five (3.8%) primary surgically treated GIST patients developed an LR, and 100 (11%) developed distant metastases (DM) only (Fig. 1).

Regarding baseline patient characteristics, patients who developed LR had significantly more often larger tumours of more than 10 cm, higher mitotic rate and tumour rupture. Patients who developed LR had more often an indication for neo-adjuvant therapy at presentation and a R1- or R2 resection. As expected, patients more often developed LR after surgery in higher-risk tumours according to the Miettinen's criteria

compared with patients who did not develop LR. Location, mutation status and histology did not significantly differ between both groups. However, patients who developed LR showed a tendency to present more often with primary non-gastric GIST (Table 1).

3.2. LR

3.2.1. Baseline characteristics

Thirty-five (3.8%) patients developed LR, with a median time to LR of 30 (IQR 8–53) months from date of surgery. Patients with an LR had a median FU of 65 (IQR 36–92.5) months from date of surgery. Median tumour size of all LR at presentation was 36 (IQR 20–102) mm. One patient was previously treated in a foreign medical centre and had LR at presentation; data about primary surgery was missing. Fifteen (42.9%) of 35 patients presented with both LR and DM. Patients who presented with DM at time of LR had metastases mostly located in the liver followed by intra-abdominal lesions (Table 2.).

3.2.2. Treatment of primary GIST

Of all patients treated with neo-adjuvant or adjuvant imatinib only, respectively, 5.2% (8/154) and 5.5% of patients (8/145) developed an LR. Patients treated with neo-adjuvant therapy only had in 32% a high-risk GIST, in patients treated with adjuvant imatinib only this was 69%. Of all patients treated with both neo-adjuvant and adjuvant imatinib, 9.7% of patients (11/114) developed an LR. Among these patients, 87.9% had high-risk GISTs.

Of all patients only treated with surgery, 1.6% (8/499) patients developed an LR and 6.2% (31/499) patients developed DM. In this group, patients had a median FU of 22 (IQR 4–56) months. Among these patients, 10.6% had high-risk GIST. In the subgroup of intermediate- and high-risk patients (20.4%, 102/499), 2.9% (3/102) and 16.7% (17/102) developed LR or DM, respectively.

In patients treated with adjuvant treatment, 2.3% (6/259) developed an LR during adjuvant therapy, of whom 4 patients were classified as high-risk GIST. Four patients had a *KIT* exon 11 mutation, 1 patient a PDFGRA mutation and 1 patient a wild-type GIST. The median time of developing LR during adjuvant therapy from start of adjuvant therapy was 7 (IQR 6.5–29) months. In addition, 5.0% (13/259) of patients developed DM during adjuvant therapy.

Of all known high-risk GIST, 37.2% (61/164) of the patients were not treated with adjuvant imatinib. Only 4.9% (3/61) of these patients developed an LR; however, 31.1% (19/61) patients developed DM. Reasons for no adjuvant treatment in this group were comorbidity, older age at time of surgery, preference of patient or treatment before the implementation of adjuvant imatinib.

3.2.3. Treatment of LR

Seventy percent (14/20) of patients with LR only were treated by surgical resection. Of all patients of whom LR was surgically resected, 10 (66.7%) had a KIT exon 11 mutated GIST, 3 wild-type GIST and 1 PDGFRA (D842V) mutated GIST (1 missing data). In 85.7% (12/14, 1 missing data) of patients, this was a radical (R0) resection. In 78.6% (11/14), surgery was combined with systemic treatment (Table 2.). Thirty percent (6/20) of the patients with LR only were not treated with surgery due to irresectable tumours, preference of patient, stable disease during treatment with imatinib due to increase dose or continuing ongoing treatment with imatinib. One patient with LR only at presentation developed DM and underwent a metastasectomy without resection of LR in addition to systemic therapy. All patients who developed LR with DM at presentation of LR (15/35) were treated with systemic therapy only (Fig. 2).

3.2.4. Development of distant metastases

Forty-three percent (15/35) of all GIST patients who developed LR presented with DM at time of LR. Seventeen percent (6/35) of patients developed DM several months after LR. Median time from LR to DM in these patients was 13 (IQR 6–37) months. One patient was treated for DM before presentation of LR (Fig. 2.).

3.2.5. Follow-up in expertise centre

A total of 31 patients with LR were followed in an expertise centre. Follow-up schedules are based mainly on regular CT scans with intervals depending on risk classification ranging from every 4 to every 12 months. The other 11.4% (4/35) patients were followed in the centre of referral, and therefore the number of scans was unknown in this group. Median FU time of the patients with LR who were followed in an expertise centre was 64 (IQR 36–90) months after surgery of primary GIST. Within this time frame, a median of 6 (IQR 2–10) scans were made during follow-up. Median time to LR was 34 (IQR 16–53) months in patients followed in an expertise centre. However, a wide range from 1 to 20 scans was performed in a time frame of 3–114 months before detection of the LR.

Twenty-eight patients (80.0%) survived after treatment of LR, with a median follow-up of 29 (IQR 14–49.5) months after presentation of LR. Nine patients (32.1%) had no evidence of disease while 19 (67.9%) patients were alive with evidence of disease.

Six patients (17.1%) died after developing LR due to GIST, while 1 patient died due to another cause (cerebrovascular accident). Almost all patients who died

Table 1
Baseline patient characteristics in primary surgically treated GIST patients.

	No recurrence (n = 777)	DM only (n = 100)	LR (n = 35)		p-Value[a]
			LR only (n = 20)	LR + DM (n = 15)	
Gender					*0.865*
Male	387 (49.8)	54 (54.0)	8 (40.0)	10 (66.7)	
Female	390 (50.2)	46 (46.0)	12 (60.0)	5 (33.3)	
Missing	*0*	*0*	*0*	*0*	
Age[b] *(median, IQR)*	64 (55–72)	60 (51–68)	62 (52–70)	62 (59–70)	*0.675*
Location					*0.094*
Gastric	542 (69.8)	44 (44.0)	10 (50.0)	10 (53.5)	
Small bowel	140 (18.0)	35 (35.0)	4 (20.0)	4 (26.7)	
Duodenal	42 (5.4)	10 (10.0)	2 (10.0)	1 (6.67)	
Rectum	36 (4.6)	11 (11.0)	2 (10.0)	0 (0.00)	
Oesophagus	4 (0.5)	0 (0.00)	1 (5.00)	0 (0.00)	
Colon	7 (0.9)	0 (0.00)	0 (0.00)	0 (0.00)	
Other	6 (0.8)	0 (0.00)	1 (5.00)	0 (0.00)	
Missing	*0*	*0*	*0*	*0*	
Histology					*0.978*
Spindle cell	567 (78.0)	77 (79.4)	16 (80.0)	11 (78.6)	
Epitheloid	76 (10.5)	7 (7.22)	0 (0.00)	1 (7.14)	
Mixed type	83 (10.4)	13 (13.4)	4 (20.0)	2 (14.3)	
Missing	*51*	*3*	*0*	*1*	
Size (cm)					***< 0.001***
≤2	73 (9.67)	2 (2.02)	0 (0.00)	2 (13.3)	
> 2 ≤ 5	284 (36.6)	17 (17.2)	5 (25.0)	0 (0.00)	
> 5 ≤ 10	270 (34.8)	34 (34.4)	6 (30.0)	3 (20.0)	
> 10	148 (19.1)	46 (46.5)	8 (40.0)	9 (60.0)	
Missing	*2*	*1*	*1*	*0*	
Presentation *(at registry)*					***< 0.001***
Localised	583 (75.0)	49 (49.0)	10 (50.0)	6 (40.0)	
Locally advanced	194 (25.0)	51 (51.0)	10 (50.0)	9 (60.0)	
Missing	*0*	*0*	*0*	*0*	
Number of mitoses					***0.002***
< 5 per 5 mm^2	510 (76.4)	38 (46.9)	10 (58.8)	3 (3.33)	
> 5 per 5 mm^2	157 (23.5)	43 (53.1)	7 (41.2)	6 (6.67)	
Missing	*110*	*19*	*3*	*6*	
Mutation					*0.289*
KIT	431 (71.5)	82 (88.2)	13 (68.4)	15 (100.0)	
Exon 9	*37*	*11*	*0*	*0*	
Exon 11	*375*	*68*	13	14	
Exon 13	*8*	*2*	0	1	
Exon 17	*4*	*0*	0	0	
Missing	*8*	*1*	0	0	
PDGFRA	110 (18.2)	3 (3.23)	1 (5.26)	0 (0.00)	
Wild-type	62 (10.3)	8 (8.60)	5 (26.3)	0. (0.00)	
Missing	*174*	*7*	*1*	*0*	
Centre of first surgery					*0.432*
GIST reference centre	579 (74.5)	64 (64.0)	14 (70.0)	10 (66.7)	
Non-reference centre	198 (25.5)	36 (36.0)	6 (30.0)	5 (33.3)	
Missing	*0*	*0*	*0*	*0*	
Margin (cm) primary surgery					***0.010***
R0	703 (92.8)	84 (85.7)	11 (68.8)	14 (93.3)	
R1	47 (6.20)	11 (11.2)	4 (25.0)	1 (6.67)	
R2	7 (0.92)	3 (3.06)	1 (6.25)	0 (0.00)	
Missing	*20*	*2*	*4*	*0*	
Tumour rupture					***0.001***
No	575 (88.7)	62 (78.4)	12 (75.0)	8 (61.54)	
Yes	73 (11.3)	17 (21.5)	4 (25.0)	5 (38.46)	
Missing	*129*	*21*	*4*	*2*	

(*continued on next page*)

Table 1 (*continued*)

	No recurrence (n = 777)	DM only (n = 100)	LR (n = 35)		p-Value[a]
			LR only (n = 20)	LR + DM (n = 15)	
Systemic therapy					***< 0.001***
No	464 (59.7)	27 (27.0)	6 (30.0)	2 (13.3)	
Neo-adjuvant imatinib	119 (15.3)	27 (27.0)	6 (30.0)	2 (13.3)	
Adjuvant imatinib	114 (14.7)	23 (23.0)	5 (25.0)	3 (20.0)	
Neo-adjuvant + adjuvant imatinib	80 (10.3)	23 (23.0)	3 (15.0)	8 (53.3)	
Missing	*0*	*0*	*0*	*0*	
Miettinen					***< 0.001***
None	60 (10.1)	2 (3.13)	0 (0.00)	0 (0.00)	
Very low	141 (23.7)	2 (3.13)	0 (0.00	0 (0.00)	
Low	178 (29.0)	6 (9.38)	4 (30.8)	0 (0.00)	
Moderate	101 (17.0)	16 (25.0)	4 (30.8)	1 (12.5)	
High	114 (19.2)	38 (59.4)	5 (38.5)	7 (87.5)	
Missing	*183*	*36*	*7*	*7*	

Other locations: mesenterium (n = 2), peritoneum (n = 2), adrenal gland (n = 1), omentum majus (n = 1) and adnex (n = 1).
[a] p-Value for no recurrence (without LR and DM; n = 777) versus total LR group (n = 35). p-value < 0.05 is considerd as significant.
[b] Age at diagnosis.

(86%) had DM at presentation of LR. The median time of survival after presentation of LR of patients who died due to disease was 33 (IQR 17–39.5) months.

4. Discussion

In this study, primary surgically treated GIST showed a limited risk of recurrence. Fifteen percent developed a recurrence, of which only one quarter developed an LR. Patients who developed LR had more aggressive GIST with larger tumour sizes, higher mitotic count and therefore were most often classified as high-risk GIST according to the Miettinen's criteria.

According to the ESMO guidelines, an R1 margin is acceptable after treatment with neo-adjuvant therapy when R0 otherwise implicates a multivisceral resection [26]. Previous literature states that R1 margins have no effect on patient survival and the risk of recurrence [1,20,27,28]. In this study, patients who developed LR showed significant more often R1 resections compared with patients who did not develop an LR. However, a multivariate regression analysis adjusting for important prognostic factors such as Miettinen's criteria, margin and tumour rupture could not be performed due to a small sample size of patients with an LR.

The ESMO guidelines recommend treatment with adjuvant imatinib for high-risk GIST [26]. In our study, a third of the patients with a high-risk GIST according to Miettinen's criteria did not receive adjuvant therapy after surgery. The main reason for this could be that adjuvant treatment with imatinib was implemented after 2011; other reasons were comorbidity or wish of patient. As expected, this group showed a relatively higher incidence of recurrences (4.91% LR and 31.3% DM)

Table 2
Characteristics of local recurrence in primary surgically treated GIST patients.

	Total (n = 35)	LR only (n = 20)	LR + DM (n = 15)
Time to LR in months (*median, IQR*)[a]	30 (8–53)	19 (7–50)	41 (20–59)
Tumour size LR in mm (*median, IQR*)	36 (20–102)	35 (20–118)	36 (18–68)
Location DM[b]	NA	NA	
Liver			4 (26.7)
Intra-abdominal			7 (46.7)
Liver + intra-abdominal			4 (26.7)
Treatment[c]			
Only surgery	3 (8.57)	3 (15.0)	0 (0.00)
Systemic treatment	21 (60.0)	6 (30.0)	15 (100)
Surgery + systemic treatment	11 (31.4)	11 (55.0)	0 (0.00)

LR = local recurrence; DM = distant metastases.
[a] From time of surgery (n = 1 missing).
[b] DM at presentation of LR.
[c] Surgery for local recurrence (n = 1 patient with metastasectomy without resection of LR not included).

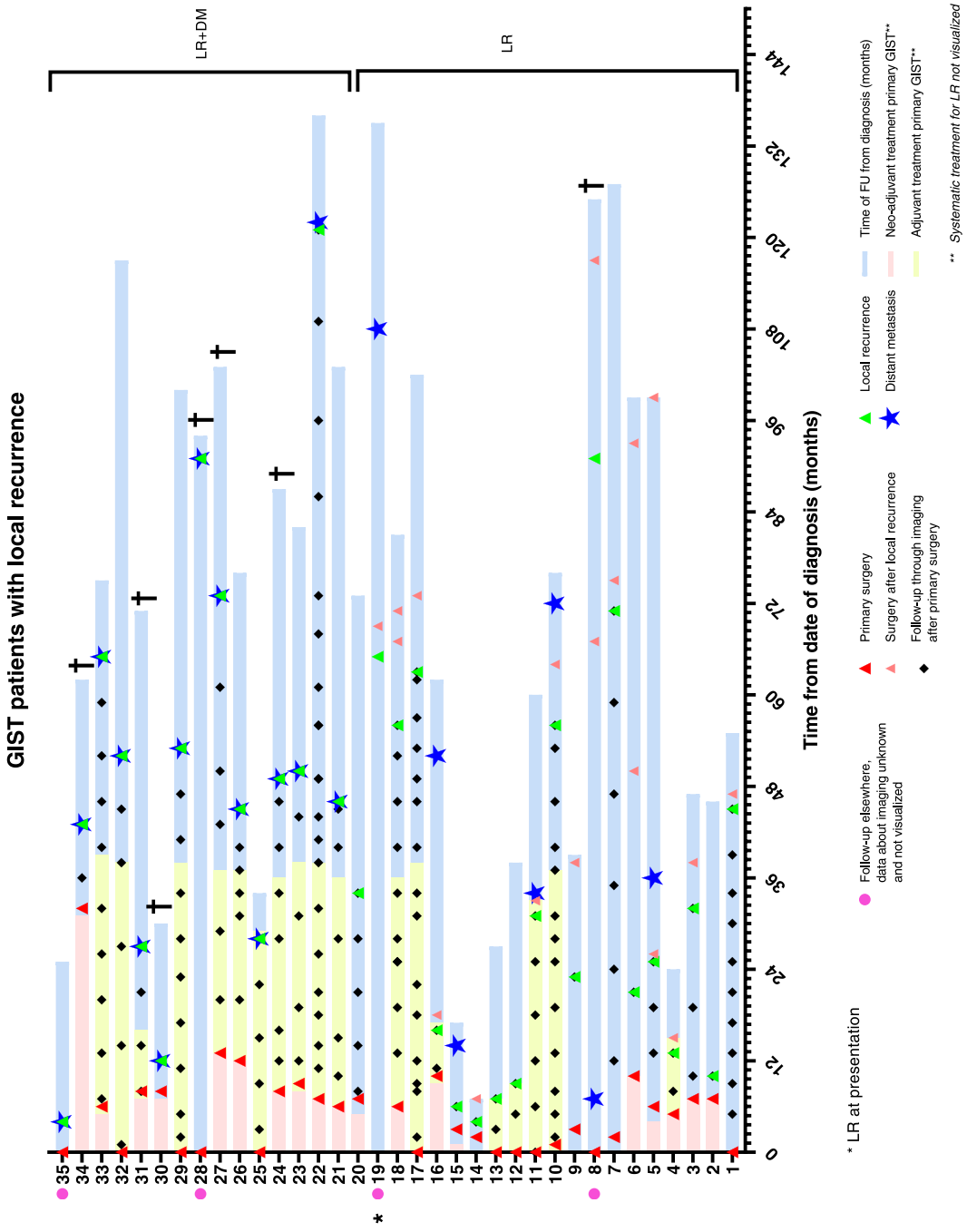

Fig. 2. Treatment and follow-up in primary surgically treated GIST patients with local recurrence. LR = local recurrence; DM = distant metastases.

compared with the total group. However, a longer FU time is also observed in these patients.

No data are available in known literature for an optimal follow-up strategy in GIST patients, and follow-up strategies differ across institutions. ESMO guidelines are therefore expert opinion based. Because of this lack of data, there seems to be a conservative tentative trend for intensive follow-up schedules in GIST patients. This could also be explained by previous literature describing a high risk of recurrence (both LR and DM) of 50% in primary surgically treated GIST [1,19–24]. However, our current study showed a significantly lower risk of recurrence of only 15%, which could be explained by the implementation of adjuvant imatinib in 2011. Patients who developed LR and were followed in an expertise centre underwent median 6 follow-up scans with a wide range of 1–20 scans. In addition, in all patients with LR, the median time to LR was 30 (IQR 8–53) months from date of surgery of primary GIST. Therefore, less intensified follow-up schedules should be considered, especially in patients who were treated with surgery only. These patients also showed less high-risk GIST compared with patients treated with (neo-)adjuvant imatinib. However, further research is needed to assess long-term data of both DM and LR rates.

Adjuvant imatinib was implemented to reduce the risk of recurrence in primary surgically treated (high-risk) GIST. Among patients who develop recurrences despite adjuvant treatment, patients with high-risk GIST most often present with recurrences 1–3 years after cessation of adjuvant treatment [26]. Therefore, patients with high-risk GIST are more intensified followed after cessation of adjuvant treatment with imatinib is completed. Also in this study, irrespective of the risk classification, most patients developed recurrence after cessation of adjuvant treatment with imatinib. According to national Dutch guidelines, patients with an indication for adjuvant therapy undergo an intensive follow-up schedule with every 6 months a follow-up CT scan during adjuvant therapy and every 4 months a CT scan within the first 2 years after end of adjuvant treatment. Our study showed that only 2.3% of the patients treated with adjuvant therapy developed LR during adjuvant therapy. A total of 5.0% of patients developed DM only during adjuvant therapy. According to this finding, a less intensive follow-up schedule of a CT scan once a year could be considered during treatment with adjuvant imatinib despite the relatively high proportion of high-risk GIST in this group. After completion of adjuvant therapy, more intensive follow-up schedules are needed, especially in patients with high-risk GIST.

Most (70%) patients with LR only could be treated with surgical resection. This was most often combined with systemic therapy. All patients with both LR and DM at presentation were treated with systemic treatment only.

Before the implementation of imatinib, poor survival with a median of 5 months was reported in GIST patients who developed LR [1]. However, in our study, only 17% (6/35) of all patients who developed LR died due to disease with a median time of survival after presentation of LR of 33 (IQR 17–39.5) months. GIST patients who developed LR who were still alive (with or without disease) in this cohort had a median time of FU 29 (IQR 14–49.5) months after development of LR. Patients who showed DM at presentation of LR appeared to have worse survival; however, due to the small sample size, a statistical analysis could not be performed.

Another limitation of this study is the retrospectively collected data, resulting in missing data which could induce selection bias. Moreover, the cohort design resulted in a wide range of 0–140 months of FU after surgery. This resulted in a median FU of 30 months and therefore no long-term conclusions could be drawn. Due to a low number of LR, a required landmark analysis for overall survival in GIST patients according to LR status and/or according to treatment of LR (surgical versus systemic treatment) could not be performed. Further research is needed to better understand long-term patterns of recurrences (both LR and DM) in patients with primary surgically treated localised GIST. Nevertheless, this national multicenter study is the largest series examining LR in primary surgically treated GIST patients.

5. Conclusion

After the introduction of adjuvant imatinib, patients with primary surgically treated localised GIST generally have a limited risk of recurrent disease and only have a small risk to develop LR. In patients with LR without DM, potentially curative treatment strategies, including surgical (re-)resection, are still possible. This study shows that less intensified follow-up schedules could be considered, especially during treatment with adjuvant imatinib.

CRediT authorship contribution statement

Roos Bleckman: Conceptualisation, Methodology, Formal analysis, Investigation, Data Curation, Writing – Original Draft. **Evelyne Roets:** Validation, Formal Analysis, Investigation, Data Curation, Writing – Review & Editing. **Nikki IJzerman:** Data Curation, Writing – Review & Editing. **Mahmoud Mohammadi:** Data Curation, Writing – Review & Editing. Han Bonenkamp: Writing – Review & Editing. **Hans Gelderblom:** Writing – Review & Editing. **Ron Mathijssen:** Writing – Review & Editing. Neeltje Steeghs: Methodology, Validation, Formal analysis, Writing – Review & Editing, Supervision. **An Reyners:** Conceptualisation, Methodology, Validation, Formal analysis, Writing – Review & Editing, Supervision. **Boudewijn van Etten:** Conceptualisation, Methodology,

Validation, Formal analysis, Writing – Review & Editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported by a research grant for the Dutch GIST Registry, which was received from Novartis (3017/13), Pfizer (WI189378), Bayer (2013-MED-12005) and Deciphera (4EE9EEC-7F19-484D-86A4-646CFE0950A5). These funding sources did not have any involvement in the conduction of this research.

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