European Journal of Surgical Oncology 45 (2019) 410–415

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Surgical and medical management of small bowel gastrointestinal stromal tumors: A report of the Dutch GIST registry

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ARTICLE INFO

Article history:
Available online 16 October 2018

Keywords:
GIST
Small bowel
Surgery
Treatment
Sarcoma

ABSTRACT

Background: A cohort of 201 patients with small bowel gastrointestinal stromal tumors (GIST) treated between January 1st, 2009 and December 31st, 2016 in five GIST expertise centers in the Netherlands was analyzed. Goal of this study was to describe the clinical, surgical and pathological characteristics of this rare subpopulation of GIST patients, registered in the Dutch GIST registry.
Methods: Clinical outcomes and risk factors of patients with small bowel GIST who underwent surgery or treated with systemic therapy were analyzed. A classification was made based on disease status at diagnosis (localized vs. metastasized).
Results: 201 patients with small bowel GIST were registered of which 138 patients (69%) were diagnosed with localized disease and 63 patients (31%) with metastatic disease. Approximately 19% of the patients had emergency surgery, and in 22% GIST was an accidental finding. In patients with high risk localized disease, recurrence occurred less often in patients who received adjuvant treatment (4/32) compared to patients who did not (20/31, $p < 0.01$). Disease progression during palliative imatinib treatment occurred in 23 patients (28%) after a median of 20.7 (range 1.8–47.1) months. Ongoing response was established in 52/82 patients on first line palliative treatment with imatinib after a median treatment time of 30.6 (range 2.5–155.3) months.
Conclusion: Patients with small-bowel GIST more frequently present with metastatic disease when compared to patients with gastric GIST in literature. We advocate for Prospective registration of these patients and investigate the use of surgery in patients with limited metastatic disease.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal malignancies of the gastrointestinal tract [1]. The annual incidence of GIST is between 11 and 20 cases per million people [2]. GISTs originate from the interstitial cells of Cajal, known as the smooth muscle pacemaker cells of the gastrointestinal tract [3]. Most frequently, GISTs originate in the stomach (60%) or small bowel (30%) [4]. GISTs develop due to driver mutations in genes coding for the tyrosine kinase receptor c-KIT (80%) or PDGFRα (10%), both expressed on the cell surface, 10% consist of wild-type tumors or rare occurring mutations in other genes [2,5].

Surgery is the only curative treatment in patients with localized disease or oligo-metastases. GISTs generally metastasize primary to the liver or within the abdominal cavity. Patients with locally

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https://doi.org/10.1016/j.ejso.2018.09.013
0748-7983/

advanced GIST who are not suitable for primary surgery can be treated in a neo-adjuvant setting with imatinib, a tyrosine kinase inhibitor, targeting KIT and PDGFRα [6]. If volume reduction is achieved, patients may become eligible for surgery. Patients with metastatic disease respond on average for 24 months on first line therapy with imatinib, but this is largely dependent on mutational status of the tumor [7]. Second line therapy consists of sunitinib, and third line of regorafenib [8,9].

Not all GISTs have the same clinical behavior [10,11]. GISTs with PDGFRα mutations generally originate in the stomach. Despite the fact that these GISTs are relatively often imatinib insensitive, they have a good prognosis since they are often detected as localized disease. Gastric GISTs have other biological and clinical properties than GISTs originating from the small bowel or duodenum as seen in the different rates in risk of recurrent disease [12].

Many papers have been published describing the treatment and characteristics of patients with GIST, however only few are available regarding the subpopulation of patients with small bowel GIST.

The clinical, surgical and pathological characteristics of a Dutch cohort of patients with small bowel GIST in the era of targeted therapy are described. The knowledge obtained from a large cohort of small bowel GISTs treated in expert centers may facilitate future clinical decision making.

Materials and methods

Patients with GIST treated in or referred to one of the five GIST centers of expertise in the Netherlands (Antoni van Leeuwenhoek Amsterdam, Leiden University Medical Center, Erasmus Medical Center Rotterdam, Radboud University Medical Center Nijmegen, University Medical Center Groningen) are retrospectively and prospectively registered in a national database since 2009 (Dutch GIST registry) [13].

Patient and clinical characteristics, pathology reports, as well as data on surgical procedures, systemic therapy, recurrence and survival are registered. Patients with a small bowel GIST treated between January 1st, 2009 and December 31st, 2016 were identified and included in this retrospective study.

Patients were categorized based on having localized or metastatic disease on CT or PET-CT scanning at time of diagnosis. After surgery, patients received adjuvant systemic treatment based on the primary tumor characteristics using Miettinen or Joensuu risk classification and follow up was performed according to international guidelines [12,14,15]. Response evaluation during systemic therapy was performed every 3, 6 or 12 months using CT scans that were reviewed by a trained radiologist in one of the expertise centers following RECIST and/or CHOI criteria.

Staining of tumor samples (CD-117 and/or DOG-1) was done according to local pathology protocols. Mutational analysis of the primary tumors was performed using Sanger sequencing and next generation sequencing. Genes tested included the most common mutated genes in GIST, KIT and PDGFRα. Statistical analysis was performed using SPSS statistical software, version 23 and R software for statistical computing and graphics.

Results

Patient characteristics

In total, 201 patients were identified in the registry (containing 878 patients) with a newly diagnosed GIST originating from the small bowel (Table 1). Patients who did not present in an emergency setting generally not experienced pain or discomfort from the tumor. Anemia was frequently diagnosed, in 72 patients (44%) at diagnosis. 31% of the patients presented with metastasized disease, all patients had intra-abdominal metastases but four patients (2%) were also diagnosed with lung metastases.

Table 1
Baseline characteristics at time of entry in the registry. Besides primary tumor size, no significant differences were present between patients with localized and metastasized disease at diagnosis (data not shown).

Baseline characteristics	No.	
Patients	201	
Male/Female	98/103	
Median age at diagnosis (year)	60.8	Range 18.5–87.5
WHO performance score at baseline		
0-1	124	
2-3	9	
Unknown	68	
Median Hb level at diagnosis (mmol/l)	7.8	Range 4.4–10.5
Tumor status at diagnosis		
Localized	138	
Metastasized	63	
Primary median tumor size (mm)	80	Range 8 -250

Pathology

Pathology reports were available of 195 patients (Table 2). Staining for CD-117 was reported of 177 samples (91%) of which 174 were positive (98%). Three primary tumors that were CD-117 negative, were DOG-1 positive. DOG-1 staining was negative in 1 of the 118 tested samples. None of the tested samples were negative for both CD-117 and DOG-1 staining. Mutational analysis was performed for 156 (80%) primary tumors. Data from diagnostic biopsies was available of 65 patients and adequate risk classification could be made in 57 of these patients (based on tumor location, tumor size and mitotic index).

Surgery

Hundred and forty five patients underwent surgery for resection of the primary tumor. Fifteen patients (10%) underwent more than

Table 2
Pathology characteristics of 201 patients. Of 175 patients a tissue sample of the primary tumor (biopsy and/or resection) was available.

Pathology characteristics	No.	%
Available reports	195	97%
Histology		
Spindle cell	140	72%
Epitheloid	13	7%
Mixed type	24	12%
Unknown	18	9%
Risk category (Miettinen [10])		
Low/medium	93	48%
High risk	97	50%
Unknown	5	3%
Immunohistochemistry		
CD-117 positive	174	89%
CD-117 negative	3	2%
Unknown	18	9%
DOG-1 positive	117	60%
DOG-1 negative	1	1%
Unknown	77	39%
Mutational analysis		
KIT exon 9	26	13%
KIT exon 11	106	54%
KIT exon 13	4	2%
KIT exon 17	2	1%
PDGFRα exon 18	0	0%
KIT and PDGFR Wild type	18	9%
Unknown	39	20%

one operation for primary tumor resection and resection of metastases (Table 3). Twenty-seven patients (19%) with metastatic disease underwent surgery. Indications for patients with metastatic disease who underwent surgery (n = 27, 35 surgeries) were resection of the primary tumor or to reach a minimal residual disease volume (n = 20), emergency setting (n = 8) or incidental diagnosis during surgery for other indications (n = 7).

Surgery in emergency setting for the primary tumor (i.e. ileus, perforation, gastro-intestinal blood loss) occurred in 30 patients which resulted in a R1 or R2 resection in 7 patients (23%).

Thirty-two patients (22%) had per-operative tumor spill, of which the vast majority (n = 22, 69%) were operated for other indications or in an emergency setting. Recurrent disease occurred in 22% of the patients (7/32) with tumor spill per-operatively with a median time to recurrence of 26.3 (range 9.7–52.4) months.

Systemic treatment

In total, 141 patients received systemic treatment, 23 in neo-adjuvant, 49 in adjuvant and 82 patients in palliative setting. First line systemic treatment consisted in 140 patients of imatinib (neo-adjuvant/adjuvant and palliative). Two patients switched early to sunitinib due to adverse events related to imatinib (nausea and orbital cellulitis with neutropenia). Twenty-two patients were treated with sunitinib as second line treatment and 12 patients were treated with regorafenib as third line treatment.

Patients treated with curative intention

Of patients with localized disease (n = 138), 110 patients (80%) directly underwent surgery for resection of the primary tumor. Fourteen patients underwent surgery following neo-adjuvant treatment (n = 23) after a median of 7 (range 1–11.5) months. Nine patients did not undergo surgery. No progressive disease was detected during neo-adjuvant treatment (partial response = 10, stable disease = 13). Three patients had to interrupt neo-adjuvant treatment because of nausea, and restarted at a lower dose. Median primary tumor diameter decreased from 99 mm (18–250 mm) to a median of 78 mm (range 18–190 mm) during neo-adjuvant treatment.

Disease recurrence was detected in 31 patients after surgery with curative intention after a median time of 20.6 (range 0–210) months. Eight patients underwent second surgery for resection of the recurrent tumor, 26 patients received also palliative systemic treatment (five patients did not receive any treatment).

In patients with high risk tumors (n = 63) adjuvant treatment was administered to 32 patients. Recurrent disease was detected in four (13%) patients treated with adjuvant treatment and in 20 patients without adjuvant imatinib (65%, $p < 0.01$). Six patients received neo-adjuvant treatment as well as adjuvant treatment.

Of 138 patients treated with curative intention, 126 patients are alive after a median follow up of 48.6 (range 24.5–414.5) months. Twelve patients died after a median time of 26.3 (range 1.3–69.9) months. Five of those patients died due to not GIST related causes.

Patients treated in palliative setting

Twenty-one out of 63 patients with metastatic disease at time of diagnosis underwent surgery for resection of the primary tumor and/or metastases. Six patients underwent surgery for metastatic disease at the time of disease recurrence after intentionally curative treatment. Palliative systemic treatment was followed by surgery in five patients (after a median time of 10 (range 7–30) months). In total, 82 patients received palliative systemic therapy. All but one (patient on study medication) received imatinib 400 mg daily as first line therapy. 52 patients have an ongoing response after a median follow up of 30.6 (range 2.5–155.2) months. Progression occurred in 23 patients after a median of 20.7 (range 1.8–47.1) months and 7 patients had to stop imatinib treatment due to adverse events after a median of 3.5 (range 0.9–36.1) months. Second line therapy with sunitinib was administered in the majority of the patients with disease progression on imatinib (85%). Thirteen out of 22 patients treated with sunitinib had disease progression after a median of 5.8 (range 2.2–20.3) months, ongoing response was seen in 5 patients with a median follow up of 37.2 (range 33.9–49.6) months. Regorafenib was started in 12 patients. Two patients have an ongoing response at 30 and 31 months, disease recurrence was detected in 8 patients after a median treatment of 4.5 (range 0.5–11.5) months and two patients had to stop within one month due to adverse events.

Table 3
Surgery characteristics. Local resection involved a typical small bowel segment or wedge resection.

Surgery characteristics	No of procedures	Non-expertise center	Expertise center
Surgical resections	161	91	70
Resection primary tumor	145	89	56
Resection recurrence or metastases	16	2	14
Median age at surgery (year; range)	60 (18–84)	60 (18–83)	63 (29–84)
Reason for surgery			
Planned	90	41	49
Planned because of other disease	36	26	10
Emergency	30	20	10
Unknown	5	4	1
Type of surgery			
Laparotomy	143	77	66
Laparoscopy	11	9	2
Unknown	7	5	2
Type of resection			
Local	141	79	62
Multivisceral	14	8	6
Unknown	6	4	2
Surgery result			
R0	121	71	50
R1	13	8	5
R2	17	8	9
Unknown	10	4	6
Tumor spill	32	21	11

Of all patients who were diagnosed with metastatic disease, 52 patients (83%) are alive after a median follow up of 34.2 (range 0–107.1) months and 11 patients (17%) died after a median follow up of 29.2 (range 0.7–61.3) months.

Overall survival

Median overall survival was not reached for patients in both groups. Patients with metastatic disease who underwent surgery for the primary tumor and resection of metastases (n = 9) combined with systemic therapy did not have a better overall survival than patients who only received systemic therapy in the described cohort (Fig. 1).

Discussion

To date, limited data is available regarding the pathological features and clinical management of small bowel GIST. The largest available cohort is from 2006 and describes 906 patients with GIST of the jejunum and ileum. However, this cohort is from the pre-imatinib era and consists of all type of GISTs [11].

In our cohort 44% of the patients had anemia at diagnosis. Next to this, the most reported symptom at diagnosis was pain or a palpable mass in the abdomen. Regrettably the exact reason for presentation and the performed imaging before presentation is not registered. At first presentation, 31% of patients had metastatic disease which is relatively high as compared to GIST originating from the stomach [16]. Recent analysis of the SEER database showed 15% of gastric GIST patients having metastatic disease at diagnosis and 20% metastatic disease in small bowel GIST [17]. Unfortunately, the exact anatomical location (proximal/distal) of the tumor is not described in the registry, so epidemiological and prognostic differences between these variants cannot be made.

According to the most recent ESMO guidelines on GIST, contrast enhanced abdominal and pelvic CT scan is the investigation of choice for patients with small bowel GIST [18]. Since GISTs derive from the outer muscular layers they usually show exophytic growth. This is in contrast to the most common malignancy in the small bowel which is adenocarcinoma that usually appears as an annular lesion in the proximal small intestine [19]. For response evaluation during treatment, two different methods could be used, following the RECIST or CHOI's criteria. The assessment of lesion density is important since response to therapy is commonly reflected by a decrease in lesion attenuation due to myxoid degeneration [20].

The quality of accuracy of the diagnosis in this registry is exemplified by the fact that the combination of CD-117 and DOG-1 were positive in 100% of cases. Mutational analysis was performed mostly in primary tumor samples. Mutational analysis of metastasis or recurrent disease could be very informative with respect to tumor heterogeneity and the development of TKI resistant disease. Remarkable is the low number of wild-type tumors, where in other large series these tumors specifically occur in the small bowel [10,11].

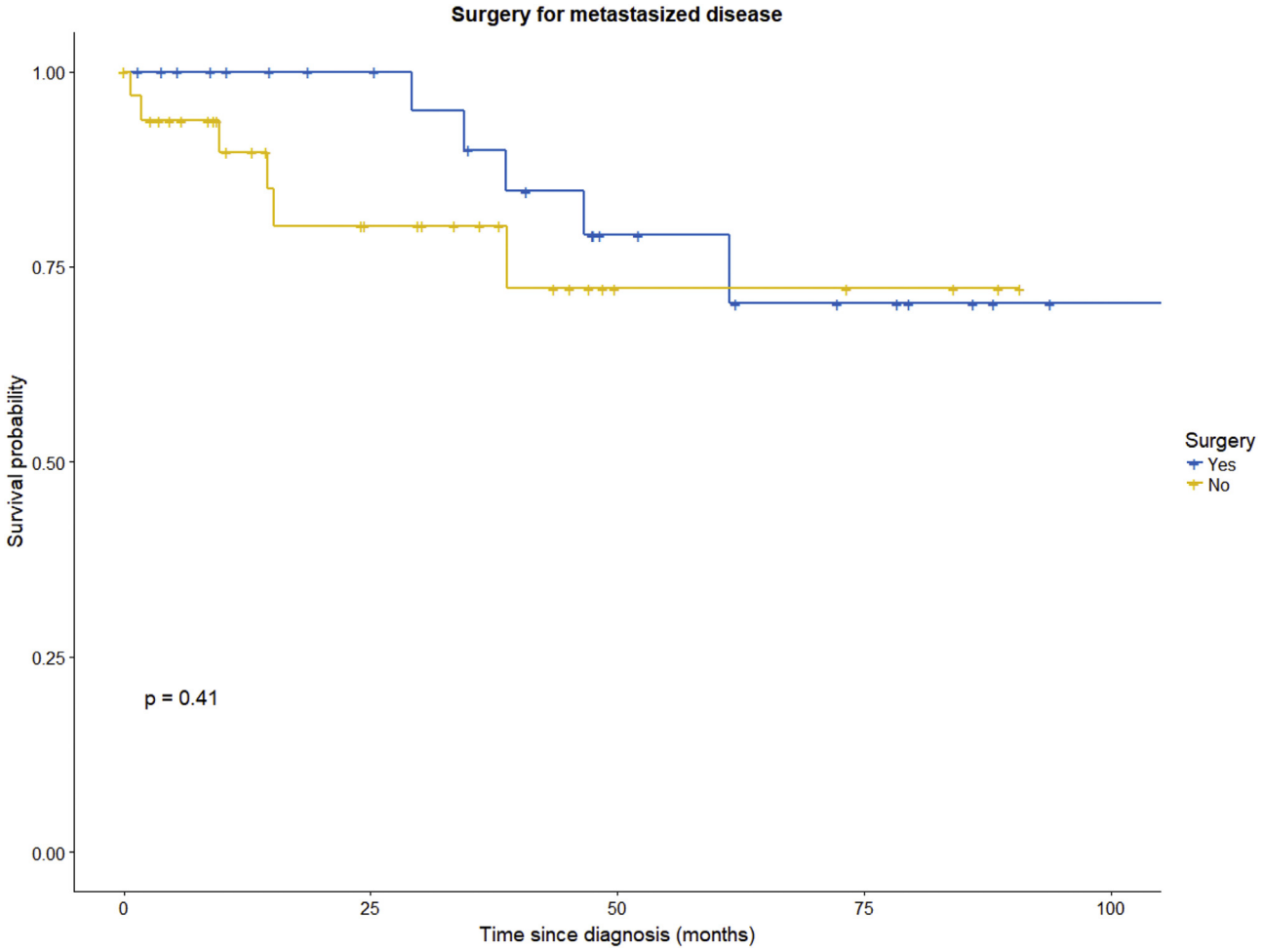

Fig. 1. Survival of patients with metastatic disease who underwent surgical resection of the primary tumor and resection of metastases.

Neo-adjuvant treatment can be safely administered to downsize the tumor size before surgery. No patients in our cohort treated with neo-adjuvant imatinib showed tumor progression or had side-effects warranting emergency surgery. Median time between start of neo-adjuvant treatment and surgery was 7.4 months, which is in accordance with international consensus that surgery should be performed within 6–12 months when maximal tumor response is reached [14]. Despite the proven effect and safety of neo-adjuvant therapy, the absolute number of patients who were treated with neo-adjuvant treatment in our cohort is relatively low [21]. This could be due to the fact that small bowel GIST occurs mainly in the large central abdominal space and primary radical resection can be more easily achieved in comparison with other anatomical locations (i.e. stomach, rectum). Neo-adjuvant treatment should be considered in patients with larger primarily resectable tumors to reduce the risk for R1/R2 resections.

Noteworthy, 61% of the patients operated with curative intent were operated in a non-expert center and afterwards referred to an expert center for further treatment. Laparotomy was the surgical treatment of choice, as GISTs of the small bowel can be large and vulnerable. So far, nine percent (3 out of 32) of the patients with pre- or per-operative tumor spill had recurrent disease, but the relatively short follow up period of the registry could have affected this favorable outcome. Most patients with tumor spill were operated in an emergency setting or for other indications therefore optimal pre-treatment diagnostics has not been performed. Chiguchi et al. report a recurrence rate of 49%–74% within two years depending on the timing of tumor spill (pre-vs preoperatively) [22]. The relatively high number of emergency surgery in the described cohort is probably due to advanced disease since early stage GISTs are known for their limited clinical symptoms.

Adjuvant treatment is indicated when the risk of recurrence is high according to Miettinen's criteria [14,23]. Of 62 patients with an indication for adjuvant treatment, only 31 patients received this. The majority of patients that did not receive adjuvant treatment had in hindsight an indication before adjuvant treatment was commonplace. According to current guidelines these patients should all be discussed with an expert center and referred for adjuvant treatment and optimal oncological follow-up. Ideally, all patients should be discussed with expert centers before surgery to optimize staging, neo-adjuvant treatment options and surgical results.

A median PFS of 20.7 months of patients on first line palliative treatment is comparable to literature where a median PFS of 20 months is reported in patients with advanced GIST treated with imatinib [24]. A recent analysis showed no significant difference in overall survival between gastric and small bowel GIST [25]. Most detected mutations in patients with small bowel GIST is in KIT exon 11. Only a few patients with KIT exon 9 or wild type received systemic treatment. Conclusions of outcome based on mutational analysis can therefore not be made. From larger studies it is known that patients with KIT exon 9 mutations have a longer PFS when treated with imatinib 400 mg twice daily [26]. The overall survival of selected patients treated with surgery for metastasized disease was not better than from patients treated with systemic therapy alone. According to earlier published patients with limited metastatic disease could be referred for surgical evaluation to increase overall survival, however this is not substantiated with our data [27]. However, these studies describe only a limited number of patients and are not specifically about patients with small bowel GIST.

To conclude, this report summarizes the clinical management and pathological characteristics of patients with localized and metastasized small bowel GIST from 2009 until 2017 in the Netherlands. Remarkable is the high number of patients who underwent emergency surgery for resection of the primary tumor. Patients with small-bowel GIST more frequently present with metastatic disease when compared to patients with gastric GIST in literature. Adjuvant treatment decreased the recurrence rate in patient with high risk tumors. We suggest to prospectively register patients with small bowel GIST in a large international database and investigate the use of surgery in patients with (limited) metastatic disease.

Financial support

The Dutch GIST registry is financially supported by unconditional research grants from Bayer, Novartis and Pfizer. PAB works on a research grant provided by the Dutch Cancer Society (KWF, Alpe D'HuZes research grant RUG 2013-6355).

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