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Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib – Analysis of prognostic factors (EORTC-STBSG collaborative study)☆

S. Bauer [a,*], P. Rutkowski [b], P. Hohenberger [c], R. Miceli [d], E. Fumagalli [e], J.A. Siedlecki [b], B.-P. Nguyen [a], M. Kerst [f], M. Fiore [g], P. Nyckowski [h], M. Hoiczyk [a], A. Cats [f], P.G. Casali [e], J. Treckmann [i], F. van Coevorden [j], A. Gronchi [g]

[a] *Department of Medical Oncology, West German Cancer Center, University of Duisburg-Essen, Essen, Germany*
[b] *Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Soft Tissue/Bone Sarcoma and Melanoma, Warsaw, Poland*
[c] *Department of Surgical Oncology & Thoracic Surgery, Mannheim University Medical Center, Mannheim, Germany*
[d] *Department of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[e] *Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[f] *Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*
[g] *Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[h] *Department of General, Liver and Transplant Surgery, Medical University of Warsaw, Poland*
[i] *Department of General, Visceral and Transplantion Surgery, West German Cancer Center, University of Duisburg-Essen, Essen, Germany*
[j] *Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*

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Abstract

Background: Long-term complete remissions remain a rare exception in patients with metastatic gastrointestinal stromal tumors (GIST) treated with IM (imatinib). To date the therapeutic relevance of surgical resection of metastatic disease remains unknown except for the use in palliative intent.

Patients and methods: We analyzed overall survival (OS) and progression-free survival (PFS) in consecutive patients with metastatic GIST who underwent metastasectomy and received IM therapy ($n = 239$).

Results: Complete resection (R0+R1) was achieved in 177 patients. Median OS was 8.7 y for R0/R1 and 5.3 y in pts with R2 resection ($p = 0.0001$). In the group who were in remission at time of resection median OS was not reached in the R0/R1 surgery and 5.1 y in the R2-surgery ($p = 0.0001$). Median time to relapse/progression after resection of residual disease was not reached in the R0/R1 and 1.9 years in the R2 group of patients, who were resected in response. No difference in mPFS was seen in patients progressing at time of surgery. Conclusions: Our analysis implicates possible long-term survival in patients in whom surgical complete remission can be achieved. Incomplete resection, including debulking surgery does not seem to prolong survival. Despite the retrospective character and likely selection bias, this analysis may help in decision making for surgical approaches in metastatic GIST.

Keywords: Gastrointestinal stromal tumor; Surgery; Metastatic disease; Survival; Imatinib

Introduction

Gastrointestinal stromal tumors (GIST) are the most common sarcomas of the gastrointestinal tract and are characterized by constitutive activation of the KIT or PDGFRA

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* Corresponding author.
E-mail address: sebastian.bauer@uk-essen.de (S. Bauer).

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receptor tyrosine kinases.[1] Localized GIST represents a potentially curable disease if complete resection can be achieved. However, the risk of a metastatic spread substantially increases with size, growth rate (as measured by mitotic counts) and primary anatomic location outside the stomach – regardless of effective local tumor control.[2] The adjuvant treatment with imatinib may improve overall survival (OS) but may not prevent a predetermined relapse.[3] Sequential treatment with tyrosine kinase inhibitors has more than tripled the median survival of metastatic and/or inoperable GIST which was estimated 18 months in the pre-imatinib era[4,5] and a small subset of patients even remains continuously stable on imatinib. However, the vast majority of patients eventually progresses and dies of their disease.

Surgical removal of metastases may cure a subset of patients with colorectal cancer or other soft tissue sarcomas but most oncological teams would advise against the same procedure e.g. in pancreatic cancer.[6] Several, mostly single-center analyses have shown that metastasectomy in GIST is safe and perioperative morbidity low, at least in those patients that do not have a generalized tumor progression.[7–10] Macroscopic complete resection in patients responding to imatinib was associated with long-term progression-free survival while patients who were operated at time of progression often relapsed briefly after intervention indicating a limited window of opportunity for meaningful surgical interventions. On the other hand imatinib cannot be stopped even after surgical complete remission, indicating that surgery has an ancillary role – if any – in achieving durable disease control in metastatic patients. In addition the risks of postoperative complications need to be taken into account when deciding for metastasectomy as severe postoperative abdominal complications may hamper the obligatory imatinib continuation.

However, the lack of any randomized trial on the role of surgery in this setting precludes unequivocal recommendations for surgery. We have sought to retrospectively investigate prognostic factors that may help in decision making until a prospective trial substantiates.

Methods

Patients and methods, perioperative management

A consecutive series of 239 patients with GIST's who had undergone surgery for metastatic GIST (until 2011) were reviewed (Table 1). Four large institutions, members of the EORTC Soft Tissue/Bone Sarcoma Group, participated in this retrospective study (Amsterdam, Essen, Milano, Warsaw) for which patient data was extracted from prospectively kept institutional databases. Where necessary, data was complemented through retrospective chart review. All patients had confirmed histopathological diagnosis of metastatic GIST and been treated with imatinib. In most cases (84%) patients received imatinib before metastasectomy. Nonetheless, for the analysis we included only those patients who then received imatinib within 3 months after metastasectomy. Patients were continued on imatinib after surgical procedures until progression. Data on postoperative morbidity was available in 191 patients.

Table 1
Patient and disease characteristics (FU = Follow-UP; IM = imatinib).

Total number	239
Male	122 (51%)
Female	117 (49%)
Median age at time of diagnosis	55 years (range: 9–79)
Location of primary	
Gastric	82 (34%)
Small intestine	134 (56%)
Other	23 (10%)
Location of metastases at time of metastasectomy	
Liver	60 (25%)
Peritoneum	110 (46%)
Liver and peritoneum	44 (18%)
Other	25 (11%)
Number of resection	
R0/R1	189 (79%)
R2	50 (21%)
Median age at time of metastasectomy	58 years (range: 18–81)
Median time from first IM to metastasectomy	1.1 years (0–6.7)
Median FU since diagnosis of metastases	5.3 years (0.25–22)
Median FU since first IM	5.1 years (0.4–10)
Median FU since metastasectomy	3.6 years (0.1–9.9)
Genotyping	164 patients
Exon 11 *KIT*	102 (62%)
Exon 9 *KIT*	23 (14%)
Wild-type	24 (15%)
Other	15 (9%)

End points and statistics

Prognostic factors investigated included sex, status of resection, location of metastases, mutational status, number of resected lesions, and remission status at the time of metastasectomy. With regard to the status of resection patients were divided into two groups comparing those in whom complete macroscopic resection [R0 plus R1] was achieved with those in whom residual macroscopic disease was left [R2]). Intra-operative rupture was defined as R2-resection. The remission status was defined as remission (non-progressive disease) versus progressive disease. Patients were classified as progressive when either new lesions occurred or an undisputable increase in size was observed. This includes patients with less than 20% increase in size as per RECIST, For the multivariate analysis, the number of resected metastases was divided into patients with 1 metastasis versus those with 2–4 and more than 4 resected metastases.

Progression-free survival (PFS) was calculated as the length of time from both the beginning of imatinib treatment for metastatic disease or from the date of surgery to the date of documented progression of residual disease, recurrent disease or death from any cause, whichever