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Role of operative therapy in treatment of metastatic gastrointestinal stromal tumors☆

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ABSTRACT

Background: Operative resection of metastatic gastrointestinal stromal tumors (GIST) is controversial. Current treatment strategies rely on the response to tyrosine kinase inhibitors (TKIs), with resultant individualization of operative intervention. We investigated the role of operative therapy in patients with metastatic GIST.

Methods: This retrospective cohort study included all consecutive patients treated for metastatic and/or recurrent GIST from January 2002 to June 2011. The patients were stratified by the use of operative therapy and disease response to TKI therapy. Kaplan-Meier survival analyses with log-rank comparisons tested the effects of operative therapy and the response to TKIs on survival.

Results: Of the 438 patients treated for GIST during the study period, 87 (median age 61 y, interquartile range 50–71; 55% male) had metastatic GIST (84% metastatic, 3% recurrent, and 13% metastatic and recurrent). Of these patients, 54 (62%) underwent operative exploration. Subtotal resection for palliative debulking (R2 resection) were performed in 19 patients; 32 patients underwent R0 resection. Operative intervention was associated with improved overall survival (OS) compared with systemic therapy alone (1 y OS, 98% *versus* 80% and 5-y OS, 65% *versus* 11%, respectively; $P < 0.001$). A TKI was used before resection in 32 patients. The disease response was partial in 13 patients, stable in 10, and progressive in 9. The 1- and 5-y OS and progression-free survival were strongly associated with the preoperative response to TKI and an R0 resection (all $P \leq 0.002$).

Conclusions: Among patients with metastatic GIST, preoperative response to TKI therapy and margin-negative resection were strongly associated with improved progression-free and OS.

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1. Introduction

The role of operative resection in patients with metastatic gastrointestinal stromal tumors (GISTs) remains investigational [1–3]. Historically, tumor metastases or recurrence have conferred a high likelihood for tumor progression and poor prognosis even after complete resection [4,5]. Since the development of tyrosine kinase inhibitors (TKIs) in the early 2000s, the focus of treatment of patients with advanced disease has shifted to medical therapy.

GISTs arise along the gastrointestinal tract as a result of activating mutations in one of the protein tyrosine kinase receptors: KIT (CD117) or platelet-derived growth factor receptor-α (PDGFRA). Imatinib mesylate and sunitinib malate, approved by the Food and Drug Administration in February 2002 and January 2006, respectively, actively block the KIT and PDGFRA receptors and inhibit tumor growth [2,6]. Subsequent level 1 data have supported the use of imatinib to improve recurrence-free survival after resection of primary GIST and to achieve significantly longer progression-free survival (PFS) among patients with advanced unresectable or metastatic GIST [7,8]. However, not all GISTs respond to TKI therapy, and approximately 20% of patients do not tolerate specific TKI agents [2,9,10]. In addition, different exon mutations, wild-type status, and the development of tumor mutations during therapy can result in treatment resistance to TKIs [2,11,12].

Resection remains an option for patients with metastatic GIST. Previous, single-institution reports have demonstrated a benefit from resection for patients with stable disease or limited progression during TKI therapy and suggested a lack of benefit for patients with disease progression during imatinib therapy [6,13]. Our aim was to examine our experience with operative therapy in patients with metastatic GIST, focusing on the effect of the preresection tumor response to TKI on PFS and overall survival (OS) in patients treated with operative metastasectomy.

2. Methods

2.1. Patients and measures

The Mayo Clinic institutional review board reviewed and approved the present study protocol. All consecutive patients treated at the Mayo Clinic (Rochester, MN) for metastatic and/or recurrent GIST from January 2002 to June 2011 were included in this retrospective study. All patients had immunohistochemically confirmed GIST according to the histologic examination and CD117, CD34, or PDGFRA positivity.

The clinically relevant demographic and clinical covariates included age, sex, primary tumor site (esophagus, stomach, small bowel, colon, rectum), primary tumor size, primary tumor grade (low or high), and CD117/KIT positivity. Grade 3 and 4 tumors were categorized as high grade. CD117 and PDGFRA exon mutational analyses were not routinely performed during most of the present retrospective study period and were not included as covariates. The tumors were classified as metastatic or recurrent, or both. Local recurrence was defined according to the presence of tumor at the anatomic site of the previous resection. The temporal affiliation between metastatic presentation and the original diagnosis was ascertained. Metastatic sites were classified as liver, peritoneal surface, bowel, omentum, lymph nodes, bone, lung/pleura, soft tissue, and uterus or ovaries. Liver operations were categorized as ablation, wedge resection, segmentectomy, bisegmentectomy, or lobectomy. Other operative procedures included bowel resection, omentectomy, peritoneal-directed surgery (resection of peritoneal deposits or peritoneal stripping), lymphadenectomy, pulmonary/chest wall resection, soft tissue resection, and ablation. The resection status was categorized as R0, R1 (residual microscopic disease), and R2 (residual gross disease).

The premetastasectomy response to TKI was categorized as stable disease, partial response, or disease progression according to the serial preoperative cross-sectional imaging findings. Although the Response Evaluation Criteria in Solid Tumors [14] were used in the beginning of the study period, the modified computed tomography response evaluation criteria (as proposed by Choi *et al.* [15]) were used during the latter half of the study period. Imatinib was the first-line TKI agent; sunitinib was used in cases of imatinib resistance or intolerance, at the discretion of the medical oncologist. All patients were individually treated by a multidisciplinary team, including gastrointestinal/sarcoma oncologist, radiologist, and surgeon. The clinical follow-up of the study cohort was updated in July 2011. PFS was calculated from the time of operation for metastatic disease to documented progression of residual disease, recurrent disease, or patient death from any cause, whichever occurred first. OS was calculated as the interval from the diagnosis of metastatic disease to patient death from any cause.

2.2. Statistical analysis

Summary data are reported as the median and interquartile range (IQR) or percentages. Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate, and are expressed as proportions. Kaplan-Meier survival analysis with the log-rank test for between-group comparisons was used to quantify the effects of operative management and the response to TKI therapy on PFS and OS [16]. The probability of a type I error of <0.05 was considered statistically significant. Bonferroni's correction was applied to pairwise tests between the survival curves of OS and PFS estimates to adjust for multiple comparisons among patients treated with TKI before metastasectomy [17]. Log-rank $P < 0.017$ (0.05/3) was considered statistically significant for these pairwise comparisons. STATA, version 10.1 (StataCorp, College Station, TX) statistical software was used for data management and analysis.

3. Results

3.1. Demographic and clinical covariates of patients with metastatic or recurrent GIST

A total of 438 patients were treated for GIST during the study period. Of these patients, 87 (20%), with a median age of 61 y