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Metastasectomy for Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the intestinal tract. Improvements in understanding the molecular pathogenesis of GIST have resulted in novel treatment strategies combining surgery with tyrosine kinase inhibitors (TKIs). Metastasectomy in carefully selected patients who have stable or responsive disease on imatinib should be considered in the multidisciplinary setting. We review existing data on surgical cytoreduction in metastatic GIST while on targeted therapy and compare outcomes with either treatment alone.

Keywords

Gastrointestinal stromal tumor; KIT; tyrosine kinase; metastasectomy

Introduction

The annual incidence of gastrointestinal stromal tumors (GIST) is about 3000–5000 cases in the US. Ninety-five percent of GISTs harbor a gain-of-function mutation in the proto-oncogene *KIT*. In ~3% of GISTs that do not express *KIT*, an activating mutation is found in the tyrosine kinase receptor PDGFRA. These mutations result in ligand-independent constitutive activation of KIT and PDGFRA resulting in abnormal cell growth and survival. The approval of imatinib, which binds to the extracellular domain of KIT and PDGFRA, revolutionized the management of this disease in 2002 [1]. Even with response rates of up to 80% with imatinib, surgery remains the only chance of cure. Despite complete resection, approximately 30% of GISTs will recur within a median of 2 years [2]. Local recurrence is rare and most recurrences are disseminated and frequently involve the liver and peritoneal lining. Until recently, the only feasible option for management of metastatic or recurrent GIST was tyrosine kinase inhibitor (TKI) therapy. Median overall survival for patients with metastatic GIST on imatinib is 5 years [3]. Increasing data suggests that metastasectomy in combination with TKIs may increase progression-free and overall survival in highly selected patients. In this article, we will provide an evidence-based review of the role of surgery in the management of patients with metastatic GIST. We discuss selection criteria, technical considerations in performing metastasectomies, and highlight how mutational status of tumors influences decisions on whether to operate and what medical treatments to use.

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Medical management of metastatic disease

The first line of treatment for patients with recurrent or metastatic disease is imatinib. Surgery for metastatic disease in the pre-imatinib era was universally associated with recurrence and median survival of 15–20 months [4]. Chemotherapy such as doxorubicin and/or ifosfamide commonly used in other sarcomas resulted in poor outcomes with response rates of 10% and median survival of less than 2 years [5–7]. Shortly after the discovery of an activating mutation in the *KIT* proto-oncogene in GIST [8], imatinib was tested in patients with advanced disease and found to have dramatic response rates in over 50% of the cohort [9]. The optimal dose of imatinib (400mg vs. 800mg/day) has been tested in two phase III trials [10,11]. While both doses resulted in equivalent response rates and overall survival, the 800mg/day dose was associated with more side-effects. Subsequent mutation analysis revealed that patients with an exon 9 mutation experienced longer progression-free survival (PFS) with 800mg/day [12]. Because the toxicity of imatinib is dose dependent [13], current guidelines suggest initiating treatment at a dose of 400mg/day, reserving 800mg/day as a starting dose for patients with metastatic GIST and a confirmed mutation in exon 9. In patients on 400mg/day, dose escalation to 800mg is considered if progression has been documented and toxicity is acceptable. Trials of imatinib in metastatic GIST are shown in Table 1. Lifelong treatment with imatinib is recommended in patients with responsive GIST due to the increased likelihood of disease progression when the drug is stopped [14]. Even in the setting of progressive disease on imatinib, the NCCN task force recommends continued therapy as a component of best supportive care to limit the growth of sensitive clones i.e. tumors that are still sensitive to imatinib [15].

Rationale for surgery as part of multimodality treatment

Surgery alone is of limited value in treating recurrent or metastatic GIST. In a study of 94 patients who presented with metastatic disease, complete gross resection was possible in only 30% and the median survival of those treated with surgery alone was 19 months [16]. While imatinib is not curative, up to 80% of patients with metastatic disease exhibit some response or stable disease on the drug [9,17]. This creates the opportunity for surgery to be combined with TKI therapy in order to improve outcomes. Moreover, lesions responding to TKI therapy by imaging exhibit a complete pathologic response less than 5% of the time [18,19], suggesting that medical management is only part of the optimal treatment strategy. Another reason to consider surgery for advanced GIST is that while most patients respond initially to imatinib, the majority develop acquired resistance. The median time to resistance is 2 years [3] and the predominant mechanism is through secondary mutations in *KIT* [20]. By reducing the tumor burden, surgery may delay the time to development of acquired resistance to imatinib. After surgical cytoreduction, fewer cells are exposed to imatinib thereby decreasing the likelihood and rate of any remaining cells to develop resistant mutations. In appropriately selected patients, the combination of surgery and TKI therapy has been associated with some cures and delays in the development of secondary resistance to imatinib [21,22]. In contrast, only about 20% of patients with metastatic GIST on imatinib therapy alone remain progression free at 5 years [3].

Surgery may provide palliation in certain patients with advanced disease who experience high-grade bowel obstructions or perforation. In some situations, continued growth of lesions on TKI therapy can result in hemorrhage that fails to cease with supportive care. While endoscopic procedures or embolization can occasionally help, metastasectomy of the bleeding lesion is often necessary.

Patient selection and outcomes after metastasectomy

While the rationale for combining surgery with medical therapy in patients with advanced disease exists, patient selection is of utmost importance. Table 2 summarizes retrospective studies in which surgery followed TKI therapy for patients with metastatic disease. The first large study to investigate outcomes after surgery in patients with disseminated disease found that survival after metastasectomy was associated with disease status on imatinib [21]. Sixty-nine patients were categorized into three groups; 1. Patients with stable disease, defined as lesions that appear unchanged or decreasing on serial CT scans; 2. Limited progression which includes few lesions that are increasing in size but still appear resectable on imaging; 3. Generalized progression in which multiple foci are increasing on TKI therapy such that complete gross resection may not be possible. As expected, rates of complete gross resection decreased from groups 1–3 as did overall survival. Patients with stable disease experienced a one-year survival rate of 95% whereas those with limited progression and progressive disease had 86% and 0% survival respectively. Not only did these data suggest that surgery may improve survival in a select group of patients, it also underscores the futility of resection in the setting of progressive disease on imatinib.

Data from Memorial Sloan-Kettering Cancer Center (MSKCC) showed similar results. Patients with radiographic responsive disease on imatinib fare best in terms of progression-free survival (PFS) after metastasectomy [22]. Three groups were identified from a cohort of 40 patients; those with responsive disease; focal resistance (defined as 1 lesion increasing on imatinib); and multifocal resistance (>1 lesion enlarging on imatinib). At the time of surgery, grossly negative margins were achieved in 85%, 46% and 29% of patients respectively. After a median follow up of 15 months, there was a significant difference in PFS between groups (responsive disease median PFS not reached, focal resistance 12 months, and multifocal resistance 5 months). The authors went on to show that despite major multi-visceral resections, patients in their cohort suffered from minimal post-operative morbidity. There were no perioperative deaths or re-explorations. This is an important factor when one considers that patients most likely to benefit from surgery are those with asymptomatic disease who are responding to TKI therapy.

Data from other single institution studies are similar [23–25]. Gronchi et al. also showed that metastasectomy can be effective in patients with lesions responding to TKI therapy. Of the 38 patients selected for surgery, 27 had disease responsive to pre-operative imatinib. Post-operative PFS was 96% and 69% at one and two years in patients with responsive disease, whereas none of the 8 patients with progressive disease were alive 1 year after surgery [26]. The authors went on to show that patients who recurred after complete resection of metastatic lesions seemed to do so because of discontinuation of therapy in the post-operative setting rather than acquisition of new mutations.

Despite the inherent biases that accompany small retrospective, single institution studies, these data do suggest that well-selected patients with stable or responsive disease on imatinib may benefit from surgical resection. Alternatively, it can be argued that surgery had no bearing on survival and the data simply reflect selection of patients with better biology that would have fared just as well with medical therapy alone. The answer to whether resection combined with TKI therapy truly confers a survival advantage awaits a randomized controlled trial. After a defined period of TKI therapy (e.g. 6–9 months), patients with resectable lesions that are stable or responding by cross sectional imaging should be randomized to surgery or continued medical therapy. Surgical patients would resume TKIs as soon as feasible after surgery. Endpoints would include progression-free and overall survival. Additional exploratory endpoints to consider are differences in development of secondary resistance to imatinib and response rates to second line agents such as sunitinib. Randomized trials that aim to address some of these issues in patients with metastatic disease have encountered poor accrual in Europe. In China, a small prospective study randomized 41 patients with metastatic GIST to the liver to imatinib alone versus imatinib followed by surgery and then additional imatinib [27]. Patients were followed for 36 months. The one and three year survival rates were higher in the surgery group when compared with the imatinib only group (100% and 89% vs. 85% and 60%).

The only prospective US study to investigate the role of preoperative imatinib in the patients with advanced GIST is a phase II trial conducted by the RTOG 0132 [28]. Albeit small and non-randomized, the results from this prospective study are consistent with the aforementioned retrospective studies that favor multidisciplinary treatment of metastatic GIST. Fifty-three patients with advanced primary or metastatic GIST had surgery after an 8–12 week period of imatinib at 600mg/day. All patients continued imatinib for 2 years following surgery. When compared with historical controls treated with imatinib alone, cytoreductive surgery following imatinib resulted in better outcomes. Five-year PFS and OS in the metastasectomy group were 30% and 68% respectively. The authors note that outcomes may have been improved further if post-operative imatinib was continued for beyond 2 years. Complications after surgery and imatinib toxicity were minimal and comparable to other reports of patients undergoing laparotomy with multivisceral resections. There was one post-operative death and one re-operation for an anastomotic leak following a colectomy. It is important to note that because all patients received two years of TKI therapy after surgery, the contribution of pre-operative imatinib to survival outcomes is not clear.

Role of surgery in imatinib resistant metastatic disease

Sunitinib malate is approved as a second line agent for patients who have progressed on imatinib. Sunitinib is an oral tyrosine kinase receptor inhibitor that not only binds to KIT and PDGFRA, but also acts on vascular endothelial growth factor receptors (VEGFR1–3), Fms-related tyrosine kinase 3, colony-stimulating factor (CSF)-1R, and RET. Surgery in patients with advanced disease on sunitinib is less well defined. In one recent report by Raut et al. 50 patients underwent surgery for metastatic disease while on second line sunitinib [29]. Unlike imatinib, pre-operative response to sunitinib did not correlate with resectability or outcomes after surgery. R0 or R1 resections occurred in 40%, 64%, and 39% of patients with responsive disease, limited progression, or generalized progression respectively. In

fact, other than age, the authors were unable to determine favorable predictors of outcome following metastasectomy. While PFS and OS were relatively high (15.6 and 26 months respectively), this is more a reflection of careful patient selection among a cohort of heavily pre-treated patients with extensive disease burden. In addition, complication rates were high with 54% of patients experiencing a complication and 16% requiring re-operation. Cytoreductive surgery in patients on second line sunitinib needs to be individualized and weighed against the associated morbidity and alternate treatment options.

Mutation status in patients being considered for metastasectomy

Optimizing the response to TKI therapy prior to metastasectomy is an important tenet in the multidisciplinary management of advanced GIST. The presence and mutation status of *KIT* and *PDGFRA* provides prognostic information and can alter the treatment algorithm. The most commonly found mutations in *KIT* occur in exons 9 and 11, whereas as exons 12 and 18 are most frequently mutated in *PDGFRA*. Most GISTs with an exon 18 mutation in *PDGFRA* are resistant to imatinib whereas those with the exon 12 mutation are sensitive to imatinib. Primary resistance to imatinib is defined as radiographic tumor progression (changes in size and tumor density by CT scan) during the first 6 months of therapy. Secondary resistance occurs later in the course of imatinib therapy (>6 months) most often as the result of a second mutation in a different region within the kinase domain of *KIT* or *PDGFRA*. Most GISTs that develop secondary resistance to imatinib have a primary mutation in *KIT* exon 11 and then develop an exon 13, 14 or 17 *KIT* mutation.

Phase III trials have shown that when compared with exon 9 mutant or wild-type (WT) GIST, patients harboring the more commonly seen *KIT* exon 11 mutation respond more favorably to imatinib and have higher rates of PFS and OS [12,30]. Patients with WT GIST that lack a mutation in *KIT* and *PDGFRA* have worse outcomes with limited response to imatinib [31].

When considering surgery for patients with advanced small bowel GIST, mutation status is particularly important. Although rare, *KIT* exon 17 mutations are most frequently seen in small bowel tumors and may exhibit primary resistance to imatinib [32]. Ineffective TKI therapy in these patients may result in loss of a window of opportunity during which metastasectomy may provide some benefit. In the absence of an exon 17 mutation, the dose of imatinib is an important consideration for patients with advanced small bowel disease. These tumors often harbor an exon 9 mutation that is more responsive to higher doses of imatinib. In a study on 377 patients with metastatic GIST, Debiec-Rychter et al. found that PFS for patients with exon 9 mutations was significantly higher on 400mg twice/day when compared with 400mg daily [12]. In addition, patients who crossed over to a 400mg twice-daily dose had a 57% response rate when compared with 7% for those with an exon 11 mutation. Ensuring patients with a small bowel exon 9 mutation have received maximal response on appropriate imatinib dosing could limit tumor progression and increase the success rate of subsequent surgery.

Mutation status has also been shown to affect response to sunitinib therapy in patients with imatinib resistance. Heinrich et al. showed in 78 patients that the clinical activity of sunitinib

is influenced by both the primary and secondary mutation status in three of the most commonly seen mutations [33]. Both PFS and OS were highest in GIST patients with exon 9 mutations when compared with exon 11 and *WT/PDGFRA* mutations. PFS and OS were longer for patients with secondary *KIT* exon 13 or 14 mutations than for those with exon 17 or 18 mutations.

Technical considerations in patients undergoing metastasectomy

CT often underestimates the disease burden in cases of advanced disease. In contrast to localized tumors, surgery for metastatic disease often requires multi-visceral resection. A systematic exploration of the entire abdomen is necessary to identify all radiographically occult nodules. The two most common sites of intra-abdominal spread are the peritoneal surfaces and the liver. In the absence of known liver disease based on pre-operative imaging, intra-operative liver ultrasound is not mandatory. Gastric GISTs have a propensity to spread to the lesser sac and rectal GISTs often spread to the recto-vesical and recto-vaginal spaces. Careful handling of tumors is important to limit tumor rupture especially in lesions that have undergone cystic degeneration or necrosis based on pre-operative CT scans. In the event of tumor rupture at the time of surgery, limiting field contamination with the use of suction and laparotomy pads is critical. Omentectomy and peritoneal stripping are often required. Moreover, in contrast to primary tumors that tend to push adjacent organs, metastatic deposits are often adherent to surrounding structures and can seldom be peeled off with negative margins. Formal lymphadenectomy is not required although enlarged nodes should be removed if encountered at the time of surgery. Liver metastases tend to be bilobar and can preclude standard hepatectomy. The use of intra-operative liver ultrasound can optimize parenchyma-preserving surgery and identify additional radiographically occult hepatic lesions. The use of radiofrequency ablation as an adjunct to hepatectomy for metastatic GIST has been reported [34]. Hepatic artery embolization is occasionally used [35]. Liver transplantation is not considered a standard approach to treating metastatic GIST despite reports of success using this technique in a small case series [36]. While laparoscopy for the management of primary gastric GISTs has been shown to have equivalent oncologic outcomes when compared with open surgery [37,38], the role of laparoscopic resection in management of metastatic disease is unknown.

Conclusions

Standard treatment for recurrent or metastatic GIST is imatinib. RCTs are needed to assess the true benefit of surgery in the setting of metastatic disease. Based on retrospective data, surgery can be considered a part of the treatment algorithm for metastatic disease in carefully selected patients who show stable disease or limited radiographic progression on imatinib. In such patients with relatively favorable biology, surgery creates the opportunity to remove clones that have become resistant to TKI therapy and may delay or prevent recurrence. Mutation status is an important consideration and the optimal duration of TKI therapy needs to be tailored to each individual based on changes in tumor size and density on serial CT scans. Scenarios in which surgery may be beneficial include, 1) patients on imatinib with stable or responsive disease amenable to complete resection; 2) resectable lesions with minimal sites of disease progression due to TKI resistance; 3) situations

necessitating emergent surgery such as perforation, high grade obstruction or refractory bleeding. Surgery does not seem to benefit patients with generalized disease progression on imatinib. Patients on sunitinib who are being considered for resection need to be aware of the risks associated with surgery and the lack of preoperative criteria that can reliably predict outcome. A treatment algorithm for patients with recurrent or metastatic GIST is shown in Figure 1.

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Figure 1.

Table 1

Trials of imatinib in metastatic GIST.

Trial	Phase	Year	Imatinib dose: mg/day (n)	Follow-up (months)	Best response %		
					PR	SD	PD
EORTC	I	2001, 2002	400, 600, 800 or 1000 (35)	8–12	51	31	8
US Multicenter	II	2002, 2004	400 (73)	34	67	16	17
			600 (74)		66	18	8
EORTC	III	2003	400 (470)	48	50	32	13
			800 (472)		54	32	9
Intergroup	III	2003	400 (350)	12	49	22	
			800 (352)		48	22	

PR, partial response, SD, stable disease, PD, progressive disease.

Note: percentages in best response column do not add up to 100 as patients were lost to follow up or dropped out of the respective trial.

Adapted from Gold JS, DeMatteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg 2006;244:176, with permission.

Table 2
Retrospective studies comparing outcomes of preoperative TKI therapy and surgery for patients with metastatic GIST.

First Author	Year	Response to imatinib (n)			Median follow-up (months)		Median PFS (months)		
		SR	FP	GP			SR	FP	GP
Raut CP ²¹	2006	23	32	14	NA		NR	7.7	2.9
DeMatteo RP ²²	2007	20	13	7	15		NR	12	5
Rutkowski P ²³	2006	24	NA	8	12		NR	NA	7
Andtbacka ²⁴	2007	21	NA	25	36		NA	NA	NA
Sym SJ ²⁵	2008	24	3	7	25.7		27.8	5.1	3.3
Gronchi A ²⁶	2007	27	8	3	29		NR	4	NA

SR, stable or responsive disease on imatinib, FP, focal progression, GP, generalized progression, PFS, progression-free survival (calculated from time of surgery), NA, not available, NR, not reached, OS, overall survival.