https://doi.org/10.1016/j.hpb.2021.11.011 HPB

ORIGINAL ARTICLE

# Hepatic metastases in gastrointestinal stromal tumors: oncologic outcomes with curative-intent hepatectomy, resection of treatment-resistant disease, and tyrosine kinase inhibitor therapy alone

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## Abstract

**Background:** Hepatic resection for metastatic GIST (mGIST) is often performed with either curative-intent or for tyrosine kinase inhibitor (TKI)-resistant lesions. The efficacy of hepatectomy for treatment-resistant lesions (TRL) is uncertain.

**Methods:** We reviewed patients with liver-mGIST treated from 2003 to 2018. Oncologic outcomes including overall (OS), post-operative progression-free survival (PFS), and post-progression OS were evaluated using Kaplan–Meier and Cox proportional hazards modeling.

**Results:** We identified n = 91 patients; 31 (34%) underwent curative-intent hepatectomy, 60 (66%) were initially managed with TKI alone, and 17 (19%) had resection of a TRL. The median follow-up for resected patients was 102 months (range 5–209 months) with 23 (25%) managed with a major hepatectomy. Patients having curative-intent hepatectomy had 72% 10-year OS following diagnosis of liver-mGIST, compared with 58% ($P$ = 0.50) for TRL resection and 41% ($P$ = 0.01) for non-resected patients. Curative-intent hepatectomy (HR 0.39, $P$ = 0.03) and age (HR 1.04, $P$ = 0.004) were independently associated with 10-year OS, but not TRL resection. TRL resection was not associated with improved post-progression OS compared to second-line TKI therapy (HR 0.61, $P$ = 0.21).

**Conclusions:** Curative-intent hepatectomy is associated with improved OS in liver-mGIST. The oncologic benefit of resecting treatment-resistant liver-mGIST compared to second-line TKI therapy alone remains unclear in the era of multi-line TKI therapy.

Received 19 August 2021; accepted 22 November 2021

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## Introduction

Gastrointestinal stromal tumors (GIST) are mesenchymal cancers deriving from the interstitial cells of Cajal.[1] The majority of GISTs are driven by oncogenic mutations in the tyrosine kinase receptor genes *KIT* and *PDGFRA*, the former being sensitive to the tyrosine kinase inhibitor (TKI) imatinib, which has dramatically improved outcomes in this disease.[2,3] Ten percent of patients with GIST have metastatic disease at diagnosis, involving the liver in two-thirds of such cases.[4,5] Additionally, the liver is a common site of recurrence following curative-intent resection of high-risk GIST. Hepatic resections for patients with GIST liver metastasis have been described and generally are associated with an overall survival benefit.[6–10] Neoadjuvant imatinib therapy, hepatic resection, and adjuvant imatinib have been shown to

This study was presented at the AHPBA, August 4th, 2021, Miami, Florida.

improve 3-year survival in both imatinib responders and non-responders compared to imatinib alone, and is generally the preferred management approach to patients with liver-metastatic GIST.[11]

Studies of patients with hepatic GIST metastases are generally limited by small cohorts, short follow-up, and grouping of patients with hepatic resections performed for separate indications: curative-intent resections in patients with oligometastatic disease and resections of emerging imatinib-resistant foci in the setting of other stable unresectable liver metastases. The theory underpinning this approach is that resection of imatinib-resistant foci may prolong the duration of response to imatinib in other lesions. In this setting, prior studies have suggested that patients with oligo-progressive disease on imatinib benefit from resection, while patients with multifocal progression do not.[12,13] Due to small cohort sizes, upfront curative-intent resection has not been well-studied compared to a "watch-and-wait" approach with aggressive resection of imatinib-resistant lesions, or whether a "watch-and-wait" approach is beneficial compared to switching to second-line therapy following oligo-progressive disease. We sought to address these unanswered clinical questions in patients treated for liver-metastatic GIST at an NCI Comprehensive Cancer Center that treats a high volume of patients with GIST.

## Methods

### Study population/patient data

A query of the prospectively maintained Knight Cancer Center Registry was performed for patients with GIST treated either medically or surgically at Oregon Health & Science University between 2003–2018; patients with synchronous and metachronous metastatic GIST to the liver at the time of first metastasis were identified. Patients were not excluded based on the presence of simultaneous peritoneal disease at metastatic diagnosis. Patients with metastases beyond the liver and peritoneum at initial metastatic diagnosis were excluded (bone n = 3, muscle n = 1). Data captured included patient demographics, clinicopathologic characteristics of primary tumors, National Institute of Health (NIH) risk categories, characteristics of metastatic disease, surgical and therapeutic treatment details, and oncologic outcomes including dates and sites of progression and dates of mortality. Staging for primary tumors was modified to reflect the 8th edition American Joint Commission on Cancer (AJCC) guidelines. All patients initiated treatment with imatinib following diagnosis of metastatic disease, and patients undergoing a curative-intent resection or resection of TKI-resistant lesions were discussed in a multidisciplinary tumor board.

No subjects were excluded from the study based on gender, racial or ethnic origin. There were no age or treatment-specific exclusion criteria. The study was reviewed and approved by the Institutional Review Board of OHSU and the Knight Cancer Institute Clinical Research Review Committee.

### Definitions

Patients were divided into groups based on receipt of hepatic resection and indication for resection. For the purposes of analysis, curative-intent resections were defined as resection or ablation of all macroscopic liver disease (R1/R0 resection), even if peritoneal disease was present. Resection of treatment-resistant lesions (TRL) were defined as resection or ablation of newly TKI-resistant lesions following an initial period of disease stability on TKI therapy of at least 3 months. Ablations were considered curative-intent with respect to the lesions ablated as GIST liver metastases are uniformly well encapsulated and therefore theoretically amenable to ablation, despite a lack of efficacy data given this rare population. Resections performed for tissue diagnosis or palliation of symptoms (n = 3) were grouped with patients not receiving a therapeutic-intent liver resection. Overall survival (OS) was measured from date of first radiographic evidence of liver-metastatic GIST, postoperative OS was measured from date of resection, and post-progression OS was measured from date of first progression. Progression-free survival (PFS) was measured in months from diagnosis of metastatic GIST until radiographic disease progression as defined by RECIST criteria,[14] while post-operative PFS was measured from date of resection. Post-progression OS (PPOS) was measured from the date of first liver progression. Liver resections were classified according to Brisbane terminology.[15] With rare exception, patients with technically resectable liver disease at diagnosis underwent curative-intent hepatectomy over the study period.

### Statistical analysis

Descriptive statistics of clinicopathologic characteristics for all patients and treatment groups were tabulated, with Chi-squared and one-way analysis of variance (ANOVA) with Tukey's *post hoc* testing used to compare groups. Kaplan–Meier and Cox proportional hazards modeling was used to analyze 10-year PFS and calculate hazard ratios (HR). Variables with $P < 0.20$ on univariable analysis were included in initial multivariable model to identify independent predictors of oncologic outcome; final multivariable models were arrived at by single backwards elimination of variables, until additional variable elimination would result in a statistically significant decrease in model fit ($P < 0.05$). In the event that all but one variable was eliminated following single backwards elimination, for simplicity only univariable statistics are shown in table form. For Kaplan–Meier and Cox modeling, all patients not experiencing the event of interest were censored at time of last follow-up. All statistics were performed using SPSS Statistics 26 (IBM Corp, Armonk, New York).

**Table 1** Clinicopathologic characteristics and treatment of patients with liver-metastatic gastrointestinal stromal tumor

| Variable | Total (n = 91) | Curative Intent (n = 31) | Resection of Treatment-Resistant Lesion (n = 17) | Debulking/Medical Therapy Alone (n = 43) | *P*-value |
|---|---|---|---|---|---|
| Age at Metastasis, Years; median [IQR] | 57 [47–67] | 58 [48–64] | 48 [40–56] | 62 [46–73] | 0.13 |
| Gender | | | | | 0.15 |
| Female | 41 (45.1) | 18 (58.1) | 5 (29.4) | 18 (41.9) | |
| Male | 50 (54.9) | 13 (41.9) | 12 (70.6) | 25 (58.1) | |
| Race | | | | | 0.53 |
| African American | 4 (4.4) | 0 (0) | 2 (11.8) | 2 (4.7) | |
| Asian | 1 (1.1) | 0 (0) | 0 (0) | 1 (2.3) | |
| White | 83 (91.2) | 29 (93.5) | 15 (88.2) | 39 (90.7) | |
| Hispanic | 1 (1.1) | 1 (3.2) | 0 (0) | 0 (0) | |
| Native American | 2 (2.2) | 1 (3.2) | 0 (0) | 1 (2.3) | |
| Primary Site | | | | | 0.11 |
| Colon/Rectum | 3 (3.3) | 1 (3.2) | 0 (0) | 2 (4.7) | |
| Esophageal | 1 (1.1) | 0 (0) | 1 (5.9) | 0 (0) | |
| Gastric | 44 (48.4) | 20 (64.5) | 3 (17.6) | 21 (48.8) | |
| Non-solid organ | 2 (2.2) | 0 (0) | 1 (5.9) | 1 (2.3) | |
| Small Bowel | 38 (41.8) | 9 (29.0) | 11 (64.7) | 18 (41.9) | |
| Unknown | 3 (3.3) | 1 (3.2) | 1 (5.9) | 1 (2.3) | |
| Primary Tumor Size, cm; median [IQR] | 8.5 [6.2–12] | 8.2 [6.3–11.0] | 10 [7.8–15.5] | 8.7 [5.8–12.5] | 0.22 |
| Driver Mutation | | | | | 0.76 |
| KIT | 58 (63.7) | 19 (61.3) | 13 (76.5) | 26 (60.5) | |
| NF-1 | 2 (2.2) | 2 (6.5) | 0 (0) | 0 (0) | |
| Not tested | 12 (13.2) | 3 (9.6) | 2 (11.8) | 7 (16.3) | |
| Other | 2 (2.2) | 1 (3.2) | 0 (0) | 1 (2.3) | |
| PDGFRA | 7 (7.7) | 3 (9.6) | 1 (5.9) | 3 (7.0) | |
| SDH | 10 (11.0) | 3 (9.6) | 1 (5.9) | 6 (13.9) | |
| Primary Tumor Grade at Diagnosis | | | | | 0.27 |
| G1 | 16 (17.6) | 4 (12.9) | 1 (5.9) | 11 (25.6) | |
| G2 | 44 (48.4) | 18 (58.1) | 9 (52.9) | 17 (39.5) | |
| Gx | 31 (34.1) | 9 (29.0) | 7 (41.2) | 15 (34.9) | |
| NIH Risk Assessment | | | | | 0.23 |
| High | 43 (47.3) | 16 (51.6) | 11 (70.6) | 15 (34.9) | |
| Intermediate | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| Low | 2 (2.2) | 0 (0) | 0 (0) | 2 (4.7) | |
| Very Low | 1 (1.1) | 0 (0) | 0 (0) | 1 (2.3) | |
| Metastatic | 45 (49.5) | 15 (48.4) | 5 (29.4) | 25 (58.1) | |
| Months of TKI Therapy Prior to Metastasis; median [IQR] | 0 [0–6] | 0 [0–0] | 6 [0–24] | 0 [0–4] | 0.41 |
| Months from Disease Diagnosis to Metastasis; median, [IQR] | 16 [0–46] | 10 [0–37] | 34 [20–48] | 14 [0–51] | 0.33 |
| Months from Metastatic Diagnosis to Surgery; median, [IQR] | 8 [5–23] | 6 [3–8] | 41 [17–67] | – | <0.001 |

(*continued on next page*)

**Table 1** (*continued*)

| Variable | Total (n = 91) | Curative Intent (n = 31) | Resection of Treatment-Resistant Lesion (n = 17) | Debulking/Medical Therapy Alone (n = 43) | *P*-value |
|---|---|---|---|---|---|
| Peritoneal Disease at Metastatic Diagnosis | 25 (27.5) | 5 (16.1) | 7 (41.2) | 13 (30.2) | 0.15 |
| Liver Metastases Distribution | | | | | <0.001 |
| Bilateral | 48 (52.7) | 6 (19.4) | 10 (58.8) | 32 (74.4) | |
| Left-sided | 13 (14.3) | 9 (29.0) | 2 (11.8) | 2 (4.7) | |
| Right-sided | 30 (33.0) | 16 (51.6) | 5 (29.4) | 9 (20.9) | |
| Size of Largest Liver Lesion at Diagnosis. cm; median, [IQR] | 3.7 [2.1–6.0] | 3.5 [2.3–5.5] | 5.9 [4.1–9.1] | 3.5 [2–7.3] | 0.29 |
| Number of Liver Lesions at Diagnosis; median, [IQR] | 2 [1–4] | 2 [1–3] | 2.5 [2–4] | 4 [2–9.5] | <0.001 |
| Peritoneal Metastasectomy During Treatment Course | 6 (6.6) | 1 (3.2) | 1 (5.9) | 4 (9.3) | 0.58 |
| Liver Procedure | | | | | <0.001 |
| Major Hepatectomy (≥4 Segments) | 28 (30.8) | 16 (51.6) | 10 (58.8) | 2 (4.7) | |
| Minor Hepatectomy (≤3 Segments) | 15 (16.5) | 11 (35.5) | 3 (17.6) | 1 (2.3) | |
| Wedge Resection | 4 (4.4) | 2 (6.5) | 2 (11.8) | 0 (0) | |
| MWA/RFA | 4 (4.4) | 2 (6.5) | 2 (11.8) | 0 (0) | |
| No Surgery | 40 (44.0) | 0 (0) | 0 (0) | 40 (93.0) | |
| Nature of Metastasectomy | | | | | <0.001 |
| Curative-Intent Primary and Metastasis Resection | 11 (12.1) | 11 (35.5) | 0 (0) | 0 (0) | |
| Curative-Intent Resection of Metachronous Disease | 20 (22.0) | 20 (64.5) | 0 (0) | 0 (0) | |
| Resection of Multifocal Progressive Disease | 3 (3.3) | 0 (0) | 0 (0) | 3 (7.0) | |
| Resection of TKI-Resistant Clone | 17 (18.7) | 0 (0) | 17 (100) | 0 (0) | |
| Never Liver Surgery | 40 (44.0) | 0 (0) | 0 (0) | 40 (93.0) | |

Abbreviations: IQR = interquartile range; TKI = tyrosine kinase inhibitor; NIH = national institute of health; MWA = microwave ablation; RFA = radiofrequency ablation.

## Results

### Clinicopathologic characteristics

Over the 16-year study period, 91 patients with GIST liver metastases were identified meeting study criteria (Table 1). The majority of patients (n = 73, 80%) were established at OHSU since initial diagnosis of metastatic disease, while 18 (20%) were referred following first progression. The median age at diagnosis of GIST liver metastasis was 57 years, with a slight male predominance (n = 50, 55%). The majority of patients were white (n = 83, 91%). Approximately half of patients had synchronous metastasis (n = 45, 49%), with the stomach (n = 44, 48%) and small bowel (n = 38, 42%) being the most common primary tumor sites. The most common driver mutations were in *KIT* (n = 58, 63.7%), *SDH* (n = 10, 11%), and *PDGFRA* (n = 7, 8%); 12 patients (13%) did not have driver mutational analysis results available for review. Patients had a median of two metastatic liver lesions at diagnosis. The liver metastases were bilateral in most patients (n = 48, 53%), followed by right-sided (n = 30, 33%) and left-sided (n = 13, 14%) only distributions. Fifty-one patients (56%) underwent hepatic resection or ablation; most were major hepatectomy (n = 28, 55%) and minor hepatectomy (n = 15, 29%), followed by hepatic wedge resection (n = 4, 8%), and thermal ablation (n = 4, 8%). There were 40 patients (44%) in the cohort who did not undergo a liver resection as part of their oncologic management of metastatic GIST. The most common indications for metastasectomy were a goal of curative-intent resection (*i.e.,* clearance of all gross and radiographic liver disease) at the time of simultaneous primary resection (n = 11, 12%) or at the time of metachronous metastatic disease (n = 20, 22%), resection of a single newly TKI-resistant lesion in the setting of otherwise stable disease (n = 17, 19%), and palliative resection of multifocal progressive disease unresponsive to therapy (n = 3, 3%). Two patients underwent ablation with curative intent due to unifocal centrally located tumors. Twenty-five (81%) of patients undergoing curative-intent hepatectomy

received pre-operative TKI therapy, for a median of 6 months (range 2–20 months). All patients receiving a curative-intent liver resection received adjuvant imatinib, and all patients undergoing resection of a treatment-resistant lesion had only been treated with imatinib prior to resection with stability of other metastatic lesions.

Among the groups of curative-intent resection (n = 31), resection of unifocal newly treatment-resistant disease (n = 17), and no resection or resection of multifocal progressive disease (n = 43) there were several relevant clinicopathologic differences. Patients undergoing resection of TRLs were more likely to have a non-gastric primary than curative-intent resections (82% versus 35%, $P = 0.003$) and non-resections (82% versus 58%, $P = 0.04$). Compared to other groups, patients undergoing curative-intent resections had fewer liver tumors at diagnosis and were less likely to have bilateral disease ($P < 0.001$ for both). Finally, patients with resection of unifocal resistant disease had significantly longer intervals from metastatic diagnosis to hepatic resection than patients undergoing curative-intent resection. Treatment groups were not significantly different by mutational status ($P = 0.76$).

## Oncologic outcomes

The median time to death or last follow-up from metastatic diagnosis was 70 months (mean 81 months, SD 57 months, range 5–240 months). The estimated OS was 130 months from diagnosis of metastatic disease (95% C.I. 86–173 months). Patients receiving curative-intent hepatectomy had an estimated 10-year OS following metastatic diagnosis of 72%, compared with 58% ($P = 0.50$) and 41% ($P = 0.01$) in patients receiving resection of a TKI-resistant lesion and medical therapy alone, respectively (Fig. 1a). Patients treated with resection of a TKI-resistant lesion did not have significantly improved OS from metastatic diagnosis compared to patients not undergoing resection ($P = 0.07$). On univariable analysis (Table 2), age at metastasis and receipt of curative-intent surgery were associated with improved 10-year OS. On multivariable analysis only older age at metastasis (HR: 1.04 per year; 95% CI: 1.01–1.06;

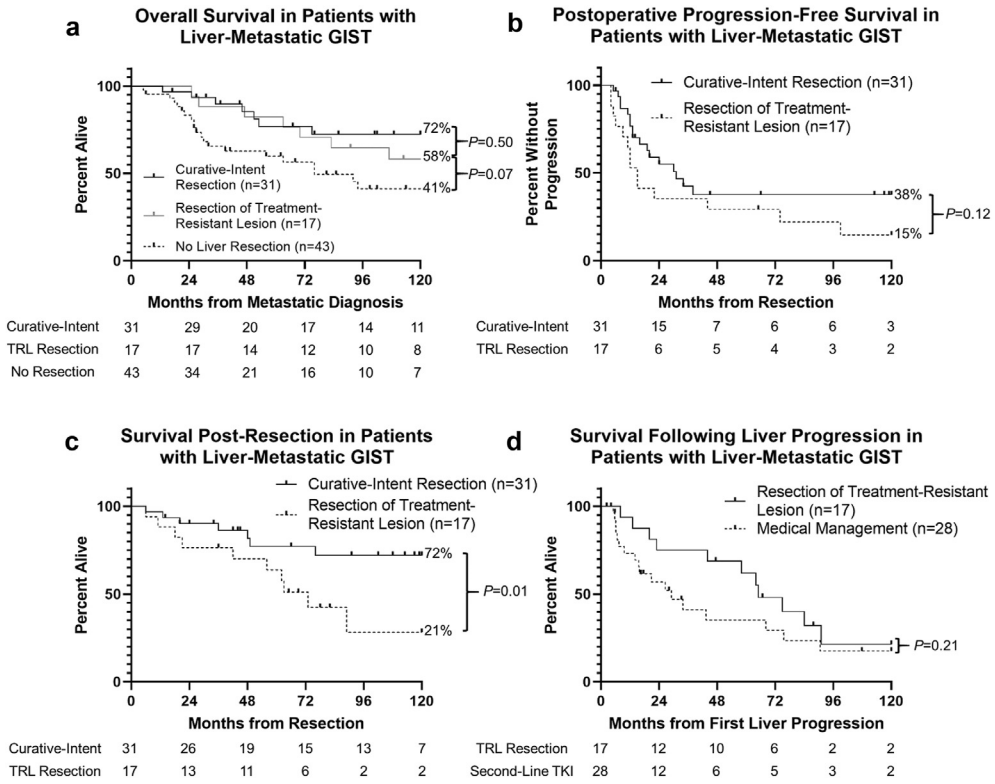


**Figure 1** Kaplan–Meier survival plots of selected oncologic outcomes in patients with liver-metastatic GIST. **Panel a)** Overall survival from metastatic diagnosis is superior for patients treated with curative-intent resection versus medical therapy alone ($P = 0.01$), but not compared to resection of treatment-resistant lesions ($P = 0.07$). Medical therapy is not associated with improved overall survival compared to resection of treatment-resistant lesions ($P = 0.50$). **Panel b)** Postoperative progression-free survival is not significantly different for patients treated with curative-intent resection versus resection of treatment-resistant lesions ($P = 0.12$). **Panel c)** Survival post-resection is improved for patients receiving curative-intent liver resection versus resection of a treatment-resistant lesion ($P = 0.01$). **Panel d)** Following first liver progression, survival is not significantly different for patients treated with medical therapy alone versus resection of treatment-resistant lesion ($P = 0.21$). Abbreviations: GIST = Gastrointestinal Stromal Tumors; TRL = Treatment-Resistant Lesion.

**Table 2** Predictors of 10-year overall and postoperative survival in patients with liver-metastatic gastrointestinal stromal tumor

| Variable | Overall Survival | | | | Postoperative Survival | |
|---|---|---|---|---|---|---|
| | Univariable HR | *P*-value | Multivariable HR | *P*-value | Univariable HR (95% CI) | *P*-value |
| Age (per year) | 1.04 (1.01–1.06) | 0.007 | 1.04 (1.01–1.06) | 0.004 | 1.02 (0.98–1.05) | 0.36 |
| Synchronous Metastasis | 1.22 (0.62–2.34) | 0.56 | – | – | 0.57 (0.21–1.52) | 0.26 |
| Largest Liver Metastasis (per additional cm) | 0.97 (0.89–1.05) | 0.45 | – | – | 1.05 (0.96–1.15) | 0.28 |
| Number of Liver Metastases | 1.03 (0.94–1.14) | 0.54 | – | – | 1.25 (1.06–1.48) | 0.01[a] |
| Bilateral Disease | 1.34 (0.68–2.64) | 0.40 | – | – | 1.36 (0.53–3.51) | 0.53 |
| Non-*KIT* Mutation | 0.68 (0.28–1.67) | 0.40 | – | – | 2.31 (0.75–7.11) | 0.14[a] |
| Concurrent Peritoneal Disease | 0.80 (0.37–1.77) | 0.59 | – | – | 1.34 (0.48–3.76) | 0.58 |
| No Resection | Referent | – | Referent | – | N/A | – |
| Resection for TKI-Resistant Disease | 0.55 (0.23–1.29) | 0.17 | [a] | – | Referent | – |
| Curative Intent Resection | 0.36 (0.15–0.84) | 0.02 | 0.39 (0.17–0.90) | 0.03 | 0.31 (0.12–0.80) | 0.02 |

Abbreviations: TKI = tyrosine kinase inhibitor; N/A = not applicable; HR = hazard ratio; CI = confidence interval.
[a] Eliminated from final model.

$P = 0.004$) and receipt of curative-intent hepatectomy (HR: 0.39; 95% CI: 0.17–0.90; $P = 0.03$) were independently associated with 10-year OS, while resection of a TKI-resistant lesion was not associated with improved 10-year OS compared to no resection ($P = 0.17$) and was eliminated from the final model.

## Post-operative progression-free survival

The median post-operative PFS in patients undergoing either curative-intent resection and resection of TKI-resistant disease was 31 months and 15 months, respectively (Fig. 1b, $P = 0.08$), while the 10-year post-operative OS was 72% and 21%, respectively (Fig. 1c, $P = 0.01$). On univariable analysis (Table 2), the number of liver lesions at diagnosis and curative-intent resection were associated with 10-year post-operative OS. On multivariable analysis, only curative-intent resection was independently associated with 10-year post-operative OS (HR 0.31 (0.12–0.80) $P = 0.02$) with the remaining variables eliminated from the model. Age, synchronous disease, size of largest liver metastasis at diagnosis, bilateral disease, and *KIT* mutational status were not independently associated with 10-year post-operative OS.

Both the number of liver lesions at diagnosis and bilateral disease were predictive of 10-year post-operative PFS and liver-PFS on univariable analysis (Table 3). Curative intent resection and patient age met criteria for inclusion in the initial multivariable model for post-operative PFS and liver-PFS, respectively. On final analysis of post-operative PFS, bilateral disease and curative-intent resection were eliminated from the model, leaving only number of liver lesions at diagnosis predictive of post-operative PFS. On final analysis of post-operative liver PFS, again only the number of liver lesions at diagnosis was predictive. Age, synchronous disease, *KIT* mutational status, and curative-intent resection were not independently associated with either outcome.

**Table 3** Univariable analysis of postoperative progression free survival and post-progression survival in patients with liver-metastatic gastrointestinal stromal tumor

| Variable | Postoperative Progression-Free Survival | | Postoperative Liver Progression-Free Survival | | 5-Year Post-Progression Overall Survival: | | 10-Year Post-Progression Overall Survival: | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age at Resection (per year) | 0.99 (0.97–1.01) | 0.20 | 0.98 (0.95–1.01) | 0.12[a] | 1.03 (0.99–1.06) | 0.09[a] | 1.02 (1.01–1.04) | 0.04 |
| Synchronous Metastasis | 1.10 (0.54–2.25) | 0.79 | 0.79 (0.31–2.03) | 0.63 | 1.58 (0.66–3.83) | 0.31 | 1.31 (0.62–2.74) | 0.48 |
| Size of Largest Liver Metastasis (per cm) | 1.01 (0.92–1.11) | 0.86 | 0.92 (0.79–1.06) | 0.24 | 0.99 (0.89–1.09) | 0.80 | 1.01 (0.93–1.10) | 0.83 |
| Number of Liver Metastases | 1.18 (1.01–1.37) | 0.03 | 1.28 (1.06–1.55) | 0.009 | 1.02 (0.89–1.16) | 0.78 | 0.98 (0.87–1.10) | 0.71 |
| Bilateral Disease | 1.62 (0.79–3.30) | 0.02[a] | 2.96 (1.20–7.34) | 0.02[a] | 1.70 (0.57–5.08) | 0.34 | 1.09 (0.48–2.48) | 0.83 |
| *KIT* Mutation | 0.76 (0.37–1.57) | 0.45 | 0.37 (0.04–3.16) | 0.36 | 0.80 (0.32–1.98) | 0.63 | 1.78 (0.73–4.35) | 0.20 |
| Resection of TKI-Resistant Disease | Referent | – | Referent | – | 0.42 (0.16–1.09) | 0.07[a] | 0.61 (0.29–1.32) | 0.21 |
| Curative-Intent Resection | 0.58 (0.28–1.18) | 0.13[a] | 0.70 (0.28–1.74) | 0.44 | N/A | – | N/A | – |

Abbreviations: GIST = gastrointestinal stromal tumor; TKI = tyrosine kinase inhibitor; HR = hazard ratio; CI = confidence interval; N/A = not applicable.
[a] Eliminated from final model.

On subgroup analysis of patients with *KIT* driver mutations treated with hepatic resection (n = 32), curative-intent resection was associated with improved 10-year post-operative PFS (HR 0.34, 95% CI 0.13–0.84, $P = 0.02$) compared to resection of a TKI-resistant hepatic lesion.

### Efficacy of hepatic resection for unifocal resistant lesion

To evaluate whether resection of unifocal TKI-resistant lesions altered outcome, we evaluated post-progression OS in patients initially managed with medical therapy only (n = 60). Of these patients, 45 experienced liver-only disease progression during the study period, with 17 patients undergoing resection of a unifocal TKI-resistant lesion followed by resumption of imatinib, and 28 patients switching to second-line therapy (sunitinib in n = 26). Progression was multifocal in all patients who did not receive resection of TKI-resistant lesion. The median post-progression OS was 44 months overall, 29 months in patients receiving 2nd-line TKI therapy, and 65 months in those receiving resection of TKI-resistant lesion (Fig. 1d). On log-rank testing, neither 5-year ($P = 0.07$) or 10-year post-progression OS ($P = 0.21$) were improved with resection of TKI-resistant lesions compared to second-line therapy. On univariable analysis, no identifiable factors were associated with 5-year post-progression OS (Table 3), and only increasing age at progression was significantly associated with worse 10-year PPOS.

## Discussion

Metastatic disease to the liver from GIST is a common occurrence, either at diagnosis or following recurrence after a curative-intent resection. Historically, patients with liver-metastatic GIST had an extremely poor prognosis. However, with modern multidisciplinary therapy consisting of hepatic resections and the availability of multiple lines of TKI therapy, survivorship past a decade is achievable even in patients who do not undergo hepatic resection of their metastatic disease. To our knowledge, the present study represents the largest investigation to date of surgical therapy for patients with liver-metastatic GIST in the imatinib era, which is further strengthened by a long follow-up period. Our results show that patients with liver-metastatic GIST derive a survival benefit from curative-intent resections compared to both TKI treatment alone and to resection of emergent TKI-resistant disease. Furthermore, we provide the largest analysis to date of the practice of resection of TKI-resistant lesions following liver progression. In this subgroup, we were unable to demonstrate an independent post-progression OS benefit compared to 2nd line therapy, although our sample size was small and not powered to detect a smaller treatment difference.

Theoretically, individual GIST metastases are separate entities derived from single clones, with an independent chance of developing a TKI-resistant mutation over time. This concept underpins the practice of resecting emergent foci of imatinib-resistance in patients with unresectable GIST liver metastases, as the presence of an "escape clone" should not affect the natural history of other metastatic foci. In practice, however, this theory does not appear to be the case. In our cohort, resection of TKI-resistant disease did not result in improved survival when measured from diagnosis, nor in the cohort experiencing disease progression after 1st-line TKI therapy. This may be due to generally poor survival in patients with liver progression on imatinib, consistent with other studies that have reported a similarly short median PFS. Cananzi et al. noted a 2-year OS following liver resection for progressive GIST of 40%,[8] while DeMatteo et al. reported a 2-year OS of 36% following resection of unifocal TKI-resistant lesions.[12] In light of past and present evidence, the oncologic benefit of this practice remains in doubt, especially in the modern era of multiple lines of TKI therapy which can provide long-term disease control.

Much is left to learn about disease biology in GIST, however emerging literature suggests that imatinib resistance and progression are not stochastic events, and that there is unmeasured biology beyond driver mutation contributing to such outcomes.[16] A more applicable concept may be that emergence of even one TKI-resistant lesion signals impending emergence of a more aggressive disease phenotype that may be present in a radiographically occult micrometastases at the time of diagnosis of the TKI-resistant lesion. If clonal escape were truly a stochastic event, one would expect a clear difference in post-progression survival following resection of a single TKI-resistant lesion, as one TKI-resistant lesion would not affect the probability of future lesions developing resistance. Instead, it is clear that while long-term PFS is possible after resection of a TKI-resistant lesion, this is the exception rather than the rule and can also be achieved with modern second and third-line therapies.

This study is limited by its foundation in a prospectively maintained database, and by the mobility of patients with metastatic GIST, who often receive medical and surgical therapies at several specialized GIST centers over the course of their disease. Consequently, a referral bias may exist where patients referred to OHSU may have baseline characteristics leading to altered survival compared to a population-based study. Additionally, while the present study contains the largest cohort to date of patients undergoing liver resection for metastatic GIST, as well as the largest cohort undergoing resection of unifocal TKI-resistant lesions, it remains limited by small sample size. In particular, there were only 17 patients who had hepatic resection of their TKI resistant liver metastasis, thereby limiting the statistical power to detect a difference between patients who were not treated with hepatic resection. We also included patients with peritoneal disease in our analysis, which may have affected the results. An analysis excluding these patients would have been underpowered. Additionally, in our experience, most patients with both liver and peritoneal metastatic disease expire secondary to liver progression, and we therefore advocate clearance of

all liver disease when feasible for this reason, although a case-by-case consideration is paramount. Finally, although positron emission tomography (PET) was often used in evaluating the metabolic activity of treated liver lesions in these patients in conjunction with CT scanning, we did not collect or report those results due to a lack of standardized definitions or decision-making algorithms based on PET compared to RECIST criteria. A management algorithm based on PET may have yielded different results.

## Conclusion

Gastrointestinal stromal tumor metastatic to the liver is a common occurrence in patients with GIST. Curative-intent hepatectomy should be pursued if all disease can be safely resected, and is associated with improved progression-free and overall survival compared to TKI therapy alone. In patients with unresected multifocal liver disease who experiencing disease progression, insufficient evidence exists that patients with unifocal liver progression have significantly improved outcomes compared to patients with multifocal liver progression, even with the receipt of resection for a treatment-resistant lesion. Additional study of the role of non-curative intent resection of oligo-progressive disease in liver-metastatic GIST is needed, given the multiple lines of TKI therapy now available to patients.

### Funding

MCH received partial funding from the following sources: GIST Cancer Research Fund, Jonathan David Foundation, VA Merit Review Grant partial salary support from a Veterans Affairs Merit Review Grant (I01BX005358), NCI R21 grant (R21CA263400).

### Conflicts of interest

Dr. Michael Heinrich receives consulting fees from Novartis, Deciphera Pharmaceuticals, Blueprint Medicines, and Theseus Pharmaceuticals. Dr. Michael Heinrich holds multiple patents on the diagnosis and/or treatment of GIST. One patent on treatment of GIST has been licensed by OHSU to Novartis. The other authors have no conflicts of interest or financial ties to disclose.

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