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Hepatic Resection for Metastatic Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

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Abstract

Background—Before the advent of tyrosine kinase inhibitors (TKIs), surgical resection was the primary treatment for hepatic gastrointestinal stromal tumor (GIST) metastases. While tyrosine kinase inhibitors (TKIs) have improved survival in metastatic settings, outcomes of multi-modal therapy comprising hepatectomy and TKIs for GIST are unknown. The objective of this study was to determine whether combination therapy for hepatic GIST metastases is associated with improved overall survival as compared to reported outcomes for surgery or TKI therapy alone.

Methods—Demographics, clinicopathologic tumor characteristics, treatments, and outcomes of patients who underwent hepatic resection at three high-volume centers from 1995 to 2010 were reviewed.

Results—39 patients underwent hepatectomy for metastatic GISTs; 27 patients received postoperative TKI therapy. With a median follow-up of 39.7 months, 23 (59%) patients experienced recurrence at a median time of 18 months. 1, 2, and 3-year overall survival was 96.7%, 76.8% and 67.9% respectively. Median survival was not reached at 5 years. Severe complication and mortality rates were 4 (10.2%) and 1 (2.5%) respectively. When controlling for confounders, postoperative TKI therapy was associated with improved survival (HR=0.04, CI 0.01–0.50, p=0.006), and extrahepatic disease was associated with worse survival (HR=9.51, 1.63–55.7, p=0.012).

Conclusions—Overall survival after combination therapy exceeds previous reports for treatment of metastatic GIST with hepatic resection or TKI therapy alone, and is significantly enhanced by postoperative TKI therapy. This study supports combination therapy for GIST liver metastases comprising surgical resection and TKI therapy to be more effective than surgery or TKIs alone.

Keywords

Gastrointestinal stromal tumor; liver resection; hepatectomy; tyrosine kinase inhibitor; imatinib

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Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the alimentary tract, accounting for 1% to 3% of all gastrointestinal tract neoplasms.[1, 2] After complete resection of the primary tumor focus, 40% of patients will recur within a median range of 18–24 months.[3] The most common sites for GIST recurrence are the liver and peritoneum.[3–5] Before the advent of effective systemic therapies, GIST liver metastases were resected when possible, with 5-year overall survival rates reported as 27–34% with a median survival of 36–47 months after liver resection.[6–8]

The emergence of tyrosine kinase inhibitors (TKIs) such as imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) has radically altered the management of GIST and sparked controversy over the role of hepatic resection for metastatic tumors.[9] The hallmark of GIST oncogenesis is expression of the constitutively active mutant tyrosine kinase c-KIT (CD117), which results from mutations in c-KIT or platelet-derived growth factor receptor-α (PDGFR-α) genes.[10–12] On immunohistochemical analysis, up to 90% of GIST tumors are reactive for CD117.[12] Imatinib specifically inhibits tyrosine kinases including abl, c-kit, and PDGFR-α by occupying the TK active site.[13] For the treatment of metastatic GIST tumors, imatinib has been highly effective, with initial response rates of up to 76% being reported.[14] However, complete responses (CR) are rare, and at least half of all patients develop resistance to imatinib within 2 years of starting treatment through the acquisition of secondary gene mutations.[15–17] In a recent observational study, the median survival for patients with metastatic GIST tumors to the liver treated with imatinib alone was only 48 months.[18]

Controversy exists in the management of GIST metastases to the liver with respect to the timing of combined systemic (i.e. TKIs) and loco-regional (i.e. hepatic resection) therapies.[4] Current surgical recommendations are extrapolated from small retrospective sarcoma studies (which include other sarcoma subtypes in addition to GIST), clinical trials designed to test the efficacy of adjuvant imatinib after primary resection, and a small randomized trial comparing imatinib monotherapy to imatinib in combination with hepatectomy.[19, 20] The National Comprehensive Cancer Network (NCCN) currently recommends surgery for limited disease progression refractory to systemic therapy or locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib.[21] In this multi-institutional study, we test the hypothesis that combination therapy for hepatic GIST metastases, including hepatic resection and systemic TKIs, will be associated with an improvement in overall survival exceeding that in reports of either therapy alone.

Methods

After obtaining approval from the Institutional Review Board at all institutions, demographics, clinicopathologic data, surgical treatments, and post-operative outcomes from patients who underwent liver resection at the Liver Cancer Center at the University of Pittsburgh Medical Center (UPMC), Johns Hopkins Hospital (JHH) and at Duke University Medical Center (DUMC) were reviewed. Most hepatic lesions were detected pre-operatively with computed tomography, magnetic resonance imaging, and/or positron emission tomography. Intraoperative ultrasonography was used to detect and localize all lesions with respect to major vessels. The extent of hepatic resection was at the discretion of the operating surgeon with the aim of achieving negative surgical margins and a liver remnant of sufficient volume to maintain hepatic function with intact vascular inflow, vascular outflow, and biliary drainage.

Data Collection

Standard demographic and clinicopathologic data were collected including sex, age, primary tumor characteristics, and liver metastases characteristics. 90-day post-operative morbidity and mortality were recorded. Post-operative complications were graded according to the Clavien-Dindo classification[29] with the following exceptions: (1) grade I complications were largely not recorded except for wound infection and ascites requiring diuresis and (2) the need for blood transfusion was not regarded as a complication. Complications grade III and above were considered severe. When available, data relating to the original GIST resection including surgery date and type, primary tumor location, size, and mitotic index were reviewed. Data on treatment related variables such as type of surgery and adjuvant therapy were obtained. Specifically, initiation dates for systemic tyrosine kinase inhibitor therapy were recorded and used to calculate time intervals between treatment modalities and locoregional therapy in the form of primary resection or subsequent liver resection. Type of hepatic resection was classified according to the Brisbane 2000 terminology.[22] Only patients who underwent resection of four or more liver segments were considered to have undergone a major hepatectomy as based on our recent report.[23] Margins were ascertained based on final pathological assessment. Date of last follow-up or date of death was collected on all patients.

Statistical Analyses

Summary statistics were obtained using established methods and presented as either percentages for categorical values or medians with 25^{th}–75^{th} percentile or interquartile ranges (IQR) for continuous variables. Comparisons for continuous variables were performed with the Kruskal-Wallis tests. The overall survival time was calculated from the date of surgery to the date of last follow-up. Cumulative event rates were calculated using the method of Kaplan and Meier.[24] Differences between survival curves were determined using the log-ranks test for equality. A Cox proportional hazards model[25] was developed to include only variables which carried a p-value ≤ 0.10 on univariable analysis in order to determine the association of each with overall survival. Predictive accuracy of the Cox model was assessed using the Harrell's C statistic, and the calibration of the Cox model was tested using the Gronnesby–Borgan goodness-of-fit statistic, with p-values> 0.20 considered to provide a good model fit.[26] Relative risks were expressed as hazard ratios (HR) with a 95% confidence interval (CI). The significance levels were set at $P<0.05$; all tests were two-sided. All statistical analyses were done using commercially available software STATA® v11.1 (College Station, TX).

Results

Demographics

From 1995–2009, 39 hepatic resections for metastatic GIST tumors were performed and comprised the study cohort. The median follow-up for surviving patients was 39.7 (0.8–120.6) months after metastatectomy, and the median patient age was 60.6 (51.5–73.8) years. The majority of the patients were male (71.8%) and Caucasian (84.6%). No patients in this study had a preoperative diagnosis of cirrhosis, and all had median laboratory values for liver synthetic and secretory function that were within normal range (Table 1).

The majority of primary GIST tumors were gastric (48.7%) or jejunal/ileal (30.8%) in origin. Although not available for all patients in the cohort, the median mitotic rate of the primary tumor was 20 (5–40) per 50 HPF (n=20) and the median primary tumor size was 10 (6–18) cm. 32/33 (96.9%) of patients with available immunohistochemistry reports were reactive for CD117. The median disease free interval (DFI) from primary resection to the detection of liver metastases was 25 (11.1–49.5) months, with six patients presenting

synchronously. The time elapsed between the primary surgery and subsequent resection for liver metastases was longer occurring at a median of 40.2 (20.5 – 64) months. 19 (48.7%) and 4 (10.3%) patients were treated with imatinib and/or sunitinib prior to liver surgery for a median duration of 18 (9–52) and 8.5 (1–15) months respectively. Although the median interval of time between primary resection and hepatectomy in patients receiving and not receiving preoperative TKI therapy was 38.7 (21.7 – 64.3) and 49.0 (12.1–62.8) months respectively (p=0.53), this difference was not statistically significant. This trend may suggest that early progressors were more likely to receive preoperative TKI therapy (Table 1).

16 of the 20 (80%) patients who did not receive preoperative TKI therapy before hepatic resection underwent their primary surgery for GIST before 2002 (the year imatinib was FDA-approved for the treatment of metastatic, CD117+ GIST tumors). Thus, most of these patients were likely not offered TKIs as surgery was still considered the primary treatment modality at the time. Of the remaining 4 liver resection patients who did not receive preoperative TKIs, 2 developed hepatic metastases within 1 year of their primary resection and opted for liver resection prior to initiating TKI therapy, 1 was intolerant of TKI therapy, and 1 was missing data. In contrast, the majority (14/19) of patients who underwent their primary resection after 2002 received TKI therapy prior to hepatic resection as part of the adjuvant therapy for their primary tumor.

At the time of surgical resection, the extent of hepatic resection was less than a hemihepatectomy (n = 20; 51.2%), a meso-hepatectomy (n = 2; 5.1%), a hemihepatectomy (n = 15; 38.5%), and an extended hepatectomy (n= 2; 5.1%). Right hepatectomy (n=13, 33.3%) and bisegmentectomy or sectionectomy (n=12, 30.8%) were the most commonly performed resections. 12 (30.8%) patients underwent a simultaneous major operation as described in detail in Table 2. Of these, 9 (23.1%) harbored extrahepatic disease which was resected concurrently with the hepatic resection. 6 (15.4%) had at least one tumor focus treated with a radio-frequency ablation (RFA) in addition to a formal surgical resection.

51.3% of patients had single liver metastases with a range of 1 to 9 tumors. The median size of the largest liver metastases was 3.5 (2.5 – 8) cm. All surgical margins including extrahepatic disease were negative (R_0) in 92.3% of patients, with the remaining 7.7% of patients having microscopically positive margins (R_1). In the cases where RFA ablation was also used, margin status was confirmed with postoperative CT scan obtained 4–6 weeks after surgery. The median blood loss was 300 (150–600) mL. 13 (33.0%) were documented as having a complication, but only 4 (10.2%) were classified as severe (Clavien Classification III-V). There was one perioperative mortality (2.5%) resulting from liver and respiratory failure. One (2.5%) patient required a second operation and 5 (12.8%) were readmitted within 90 days of the original discharge after surgery (Table 3).

In total, 27 (73.0%) of patients received postoperative TKI therapy with 2 (5.1%) patients lost to follow-up. Patients (n=24, 64.9%) received postoperative imatinib at a median of 44 (26–97) days after liver resection. A minority of patients (n= 6, 16.2%) were treated with sunitinib at a median of 409 (181–823) days after liver resection, usually in the setting of acquired resistance to imatinib therapy. 4 (10.2%) patients received additional varieties of postoperative therapy, and another 4 (10.2%) patients were intolerant of TKI therapy and thus never received postoperative TKI therapy. The patient who died perioperatively was treated with preoperative TKI therapy but died prior to receiving postoperative TKI therapy. The reasons for 6 other (15.4%) patients did not receiving post-operative TKI therapy were not available. The exact duration for each postoperative therapy was also unavailable (Table 3).

After resection, 23 (59.0%) patients suffered recurrence with a median disease free survival of 18 months. Among these 23 patients, 12 (52.2%) recurred in the liver only, 5 (21.7%) recurred at a distant site from the liver or primary tumor, 3 (13.0%) recurred in both the liver and another distant site, and 2 (8.7%) recurred in the vicinity of the original primary tumor. (Table 4). Although most patients eventually recurred, overall 1-year, 2-year, and 3-year survival rates were 96.7%, 76.8%, and 67.4% respectively (Table 5). Median overall survival was not reached at 60 months. Patients who received postoperative TKI therapy only had improved 1-year, 2-year, and 3-year survival rates of 100%, 91.7% and 91.7% respectively.

Univariable and multivariable analyses were performed to (1) define predictors of survival after hepatic metastectomy for GIST tumors and (2) determine optimal timing systemic TKI therapy in regards to liver resection. For these analyses, patients were categorized as either receiving postoperative TKI therapy or both preoperative and postoperative TKI therapy (perioperative TKI). Since only 3 patients received preoperative TKI therapy without postoperative TKI therapy, this category could not be included. On univariable analysis, postoperative TKI therapy (p=0.08, 0.01–0.66, p=0.019) but not perioperative TKI treatment (HR 2.36, 0.63–8.92, p=0.20) predicted improved survival. Neither perioperative treatment nor length of DFI significantly predicted overall survival on the univariable model (Table 6).

Other potential predictors of survival on univariable analyses meeting inclusion criteria for our multivariable model ($p \leq 0.10$) included single liver metastases, size of liver metastases, and extrahepatic disease. Multivariable analysis of potential confounding variables was performed using a Cox Proportional Hazards model with an event rate of 27.8% (10/36) and Harrell's C concordance statistic of 0.78. In this multivariate model, postoperative TKI therapy was found be significantly associated with improved survival (0.04, 0.01–0.55, p=0.006) while extrahepatic disease significant predicted worse overall survival (9.51, 1.63–55.7, p=0.012). (Table 7).

Discussion

In this multi-institutional study of hepatic resection for metastatic GIST tumors in the era of TKIs, we report a 3-year overall survival rate of 67.4%, with a median survival not reached at 5 years. In contrast, a median survival of 36–47 months and 48 months has been reported for patients treated with liver resection alone or TKI monotherapy respectively. [6–8, 18] Overall, morbidity and mortality was low for hepatectomy, with severe complication and mortality rates of 10.3% and 2.5% respectively. On univariate and multivariate analyses, patients who received only postoperative TKI therapy had the most favorable outcomes whereas extrahepatic disease at the time hepatic resection predicted worse survival.

This multi-institutional series provides further evidence that surgical resection combined with postoperative TKI therapy improves overall-survival for patients with GIST metastatic to the liver. Based on extrapolated evidence from clinical trials evaluating the timing of TKI therapy and primary resection as well as current understanding of GIST resistance mechanisms, two strategies for treating metastatic GIST tumors have been proposed in the current literature. The first, proposed by Haller et al.[27], is to treat recurrence of GIST with systemic TKIs and reserve surgery for patients who demonstrate early signs of TKI resistance such as "stagnation of tumor shrinkage" on radiographic imaging. The second, endorsed by DeMatteo et al from Memorial Sloan-Kettering Cancer Center (MSKCC) [12,13], emphasizes surgery for recurrent disease within six months of initiating TKI therapy to minimize risk of acquiring secondary mutations responsible for TKI resistance. Given that the response of GIST tumors to imatinib will generally plateau after 6 months of therapy, the premise of this strategy is the assumption that tumor debulking will delay the development

of secondary *KIT* mutations which lead to TKI resistance. [28] The MSKCC approach is further supported by a Chinese randomized, prospective trial reporting improved overall-survival in patients receiving 6 months of pre-operative TKI therapy prior to surgery as compared to those receiving imatinib alone.[20]

In this study, prolonged survival after hepatic resection for metastatic GIST was significantly more likely if TKIs were administered to a TKI naïve patient. In contrast, patients in the perioperative group who had long TKI-exposures (median 18 months) prior to surgery generally had shorter disease-free and overall survivals as compared to patients who received only post-operative TKI therapy (Tables 4,5). Thus, the results of this study suggest that the Haller approach which reserves surgery for signs of TKI resistance may compromise the potential long-term benefits of TKI therapy after hepatic resection for metastatic GIST. Furthermore, these results seem to support treatment strategies such as the one proposed by MSKCC which aim to prevent the development of secondary TKI resistance by minimizing TKI exposure prior to liver resection. However, we are limited in fully endorsing the MSKCC approach as the clinical practices in this study did not adhere to the MSKCC strategy in which hepatic resection was performed after 6 months of TKI therapy.

Complete responses of GISTs to TKIs are rare, and at least half of all patients with GIST will develop secondary resistance after approximately two years of treatment through secondary mutations in exons 13–17 of the KIT gene or, less frequently, the PDGFRA gene.[15–17, 27] Although there is no direct evidence to support that tumor debulking delays secondary TKI resistance, correlative scientific studies can lead one to hypothesize that the probability of developing a mutant, TKI-resistant subpopulation would be directed related to the number of tumors cells exposed and the duration of TKI exposure. Supporting this theory, mutational analyses of multiple biopsy/resection specimens from the same patient have shown evidence of clonal evolution and/or polyclonal secondary kinase mutations.[17] Moreover, *KIT* exon 17 mutations are rare in untreated in tumors, but develop relatively frequent in those exposed to TKIs.[29]

Based on current clinical and scientific evidence, treatment with systemic TKIs for patients with recurrent or metastatic GIST seem critical to achieve long-term survival.[30] Therefore, measures to prevent acquired resistance are vitally important. Since decreasing tumor cell TKI exposure does not seem plausible, resection when technically feasible becomes a logical strategy to minimize risk of developing secondary resistance mutations and is supported by the data presented in this report.

Several limitations to this study should be considered. First of all, the study is limited statistically by its small sample size which may result in unintentional biases in our models. Despite having a satisfactory model calibration and predictive accuracy, our multivariate analysis of pretested predictors may lead to overfitting which can yield results that may not be replicated in a larger sample population.[31] Until larger datasets become available, these analyses should be considered exploratory in nature, serving as the initial steps in determining significant statistical relationships. Second, the utilization of neoadjuvant and adjuvant TKI therapy amongst medical oncologists was variable and may impact rates of disease-free and overall survival reported here. Third, the exact rationale in determining duration of pre-operative TKI therapy prior to liver resection could not be fully determined in all cases introducing potential bias. Fourth, the duration of post-operative TKI therapy was not available; therefore the optimal duration of adjuvant TKI therapy remains unclear. Fifth, important prognostic factors for primary GISTs including mitotic rate and primary tumor size were not available for all patients and were not accounted for in the multivariable analysis. Finally, the retrospective nature of this work introduces the biases associated with all retrospective work.

Despite these limitations, this study provides further evidence to support hepatic resection in combination with systemic TKI therapy improves survival for patients with GIST liver metastases with acceptable morbidity and mortality. In light of current evidence reported both here and elsewhere, we recommend all patients with hepatic GISTs metastases be treated aggressively with both surgery and postoperative TKI therapy before clinical signs of TKI resistance become apparent.

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Table 1

Patient demographics, preoperative laboratory values, and clinicopathogical characteristics of primary gastrointestinal stromal tumors (GISTs).

Median follow-up, months(IQR) *	24.2 (6.6–62.3)
Median Age (years) (IQR) *	60.5 (51.5–73.8)
Gender, (%)	
Female	11 (28.2)
Male	28 (71.8)
Race, (%)	
White	33 (84.6)
Black	3 (7.7)
Other	3 (7.7)
Median Body Mass Index (n=28),(IQR) *	27.9 (24.7–33.8)
Median Preoperative Total Bilirubin (IQR) *	0.5 (0.4–0.7)
Median Preoperative INR(IQR) *	1 (1–1.1)
Median Preoperative Albumin(IQR) *	4.1 (3.85–4.25)
Median Disease Free Interval (months)(IQR) *	25 (11.1–49.5)
Median Time from Primary Surgery to Liver Resection (months)(IQR) *	40.2 (20.5 – 64)
Primary Site, n (%)	
Gastric	19 (48.7)
Duodenum	3(7.7)
Jejunum/Ileum	13 (30.8)
Colon/Rectum	1 (2.6)
Unknown	5 (10.3)
Median Primary Tumor Size (n=27) (cm) (IQR) *	10 (6–18)
Median Mitotic Rate/50 HPF (n=20) (cm) (IQR) *	20 (5–40)
CD117 positive (n=33), (%)	32 (96.9)
Preoperative Imatinib (%)	19 (48.7)
Median Duration of preoperative Imatinib (months), (n=18)(IQR) *	18 (9–52)
Preoperative Sunitinib (%)	4 (10.3)
Median Duration of Sunitinib (months)(Range)	8.5 (1–15)

* Interquartile Range (25%–75%)

Table 2

Surgical treatments for patient with hepatic GIST metastases.

Type of Liver Resection (%)	
Nonanatomic wedge	4 (10.3)
Single segmentectomy	4 (10.3)
Bisegmentectomy	12 (30.8)
Right Hepatectomy	13 (33.3)
Left Hepatectomy	2 (5.1)
Extended right hepatectomy	1 (2.6)
Extended left hepatectomy	1 (2.6)
Central Hepatectomy	2 (5.1)
Simultaneous Major Surgery (%)	12 (30.8)
Diaphragm Resection	1 (2.6)
Superior Vena Cava Resection	1 (2.6)
Adrenalectomy	1 (2.6)
Gastrectomy	2 (5.1)
Esophagogastrectomy	1 (2.6)
Splenectomy	1 (2.6)
Ventral/Incisional Hernia Repair	3 (7.7)
Peritoneal Tumor Resection	2 (5.1)
Small Bowel Resection	2 (5.1)
Distal Pancreatectomy	1 (2.6)
Extrahepatic disease present	9 (23.1)
Location	
Omentum	4 (10.3)
Peritoneum	4 (10.3)
Stomach	3 (7.7)
Diaphragm	1 (2.6)
Small Bowel	1 (2.6)
Concurrent Radio Frequency Ablation	6 (15.4)

Table 3

Post-operative outcomes, laboratory values, and liver metastases pathology.

Median Liver Metastasis Size (cm) (IQR) *	3.5 (2.5–8)	
Median Number of Lesions (Range)	1 (1–9)	
No. Single Lesion, (%)	20 (51.3)	
Multiple Lesions, (%)	19 (49.7)	
Margin Status, (%)		
R0	36 (92.3)	
R1	3 (7.7)	
R2	0 (0)	
Grade I	3 (7.6)	Wound disruption
Grade II ()	6 (15.4)	Subphrenic abscess, new-onset diabetes mellitus, aspiration, atrial fibrillation, wound Infection requiring antibiotics
Grade III	2 (5.1)	Biloma requiring ERCP and stent, empyema
Grade IV	1 (2.5)	Liver failure, bile leak, hepatorenal syndrome, lower GI bleed
Grade V	1 (2.5)	Liver failure, respiratory failure, death
Reoperation, (%)	1 (2.5)	
Readmission, (%)	5 (12.8)	
Peri-operative mortality, (%)	1 (2.5)	
Median Peak bilirubin (mg/dL) (IQR) *	1.4 (0.9–2.2)	
Median Days to peak bilirubin (IQR) *	2.5 (1.5–4.5)	
Median Peak INR (IQR) *	1.2 (1.1–1.3)	
Median Days to peak INR (IQR) *	2 (1–2)	
Adjuvant imatinib therapy, (%)	24 (64.9)	
Median Days to start Adjuvant Imatinib (IQR) *	44 (26–97)	
Adjuvant Sunitinib, (%)	6 (16.2)	
Median Days to Start Adjuvant Sunitinib (IQR) *	409 (181–823)	

* Interquartile Range (25%–75%)

Table 4

1, 2, 3-Year Disease Free Survival Estimates.

Survival (%)‡	1-year	2-year	3-year	p*
Overall (n=39)	63.4	34.1	26.1	
no TKI (n=7)	64.3	0	0	Referent
Any TKI therapy (n=31)	63.0	39.3	30.0	0.11
Postoperative TKI only (n=12)	63.1	39.9	34.6	0.13
Perioperative TKI (n=12)	61.9	30.9	6.2	0.25

‡Excludes 1 perioperative death.

*Log-Ranks Test of Equality

Table 5

1, 2, 3-Year Overall Survival Estimates.

Survival (%)	1-year	2-year	3-year	p*
Overall (n=39)	96.7	76.8	67.4	
no TKI (n=7)	81.6	50.2	0	Referent
Any TKI therapy (n=31)	96.6	77.4	71.9	0.005
Postoperative TKI only (n=12)	100	91.7	91.7	0.001
Perioperative TKI (n=15)	100	52.4	38.9	0.24

≠Excludes 1 perioperative death.

*Log-Ranks Testof Equality

Table 6

Univariable Predictors of Overall Survival.

	Hazard Ratio	95% CI	p-value
Patient Factors			
Age†	0.98/year	0.92–1.05	0.63
Non-white race	1.03	0.13–8.23	0.97
Male Gender	0.57	0.16–2.00	0.38
Tumor Factors			
Disease Free Interval†	1.00/month	0.98–1.02	0.99
Extrahepatic disease present	2.73	0.83–8.97	0.099
Mitotic Rate† (n=20)	1.01/mitoses	0.98–1.03	0.67
Primary size† (n=27)	0.93/cm	0.79–1.10	0.42
Single Liver Metastasis	0.24	0.05–1.11	0.067
Liver Tumor Metastasis Size†	1.07/cm	0.99–1.15	0.089
Treatment Factors			
Year of Surgery†	1.23/yr	0.95–1.60	0.12
Major hepatectomy	1.12	0.32–3.83	0.21
Simultaneous major operation	1.33	0.34–5.23	0.67
Tumor present in surgical margin	2.41	0.62–9.47	0.21
Postoperative TKI only*	0.08	0.01–0.66	0.019
Perioperative TKI*	2.36	0.63–8.92	0.20

*Referent is entire study cohort excluding one perioperative death.

†Treated as continuous variable

Table 7

Cox Proportional Hazards Model of Significant Predictors of Survival.

	Hazard Ratio	95% CI	p
Tumor Factors			
Extrahepatic Disease Present	9.51	1.63–55.7	0.012
Single Liver Metastases	0.80	0.14–4.68	0.81
Liver Metastases Size †	0.98/cm	0.88–1.10	0.78
Treatment Factors			
Postoperative TKI only *	0.04	0.01–0.50	0.006

* Referent is entire study cohort excluding one perioperative death.

† Treated as continuous variable

Event rate = 27.8% (10/36)

Harrell's C concordance statistic = 0.78

Gronnesby and Borgan Goodness of Fit Test – p=0.22