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Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: Conversion to resection and long-term outcomes

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Abstract

Purpose—Evaluate conversion rate of patients with unresectable colorectal-liver metastasis to complete resection with hepatic-arterial infusion plus systemic chemotherapy including bevacizumab.

Patients and Methods—Forty-nine patients with unresectable CRLM were included in a single-institution phase II trial. Conversion to resection was the primary outcome. Secondary outcomes included overall (OS), progression-free survival (PFS), and response rates (RR). Multivariate and Landmark analyses were performed to evaluate survival differences between resected and non-resected patients.

Results—Median number of tumors was 14 and 65% were previously treated patients. A high biliary toxicity rate was found in the first 24 patients whose treatment included Bev. The remaining 25 patients were treated without Bev. Overall RR was 76% (4 complete responses). Twenty-three patients (47%) achieved conversion to resection at a median of 6 months from treatment initiation. Median OS and PFS for all patients was 38 (95% CI: 28–not reached) and 13 months (95% CI: 7–16). Bev administration did not impact outcome. Conversion was the only factor associated with prolonged OS and PFS in multivariate analysis. On landmark analysis, resected patients had longer OS compared to those who did not undergo resection (3-year OS: 80% vs. 26%). Currently 10 of 49 (20%) patients are NED at a median follow up of 39 months (32–65).

Conclusion—In patients with extensive unresectable CRLM, the majority of whom were previously treated, 47 % were able to undergo complete resection after combined HAI and systemic therapy. Conversion to resection is associated with prolonged survival.

Introduction

There are over 140,000 cases of colorectal cancer yearly in the USA. Approximately 60% will develop liver metastases (CRLM).¹ Complete resection of hepatic-only metastases is associated with 5-year disease-specific survival rates of approximately 50%.² While most patients recur after partial hepatectomy, approximately 20% are cured.^{3,4} However, the vast majority (80–90%) present with unresectable disease⁵. Modern combination chemotherapy for unresectable CRLM rarely results in 5-year survival and is associated with a median survival of roughly 20 months.⁶ Some series have demonstrated that patients may be down-staged from an initially inoperable to a potentially resectable state,^{7–12} with similar 5-year survival rates to patients who were initially resectable.^{12–14} A significant problem with studies that have reported conversion to complete resection is their retrospective nature and a lack of clear definitions of irresectability and the response required for conversion to resection.¹⁵ Furthermore, the ability to resect extensive bilobar metastases has improved dramatically over the last 2 decades widening the scope of patients now considered for resection.^{16–21}

Hepatic-arterial infusion (HAI) chemotherapy has significantly higher response rates (RR) than systemic chemotherapy,^{22–24} and has become an attractive option for treatment of patients with unresectable CRLM. The high hepatic extraction rate²⁵ of HAI floxuridine (FUDR) limits its systemic toxicity and allows its use in combination with systemic agents. Prior phase-I and II studies from our institution have shown such combinations to be safe and to exhibit RR between 52 and 75% in previously treated patients and even higher in chemotherapy-naïve patients.^{26,27} In a previously reported retrospective analysis of patients with extensive unresectable CRLM receiving HAI and systemic chemotherapy as part of a phase I trial, we observed conversion to resection in 47% of a heavily pre-treated group of patients.^{27,28} Based on prior data demonstrating significant improvement in survival with the addition of Bevacizumab (Bev) to systemic chemotherapy, we felt that the addition of Bev to our HAI and systemic regimens was worthy of further study.²⁹ The aim of this phase-II study was to prospectively evaluate the rate of conversion to complete resection in patients with unresectable CRLM treated with HAI and systemic chemotherapy plus Bev in the context of strictly prespecified definitions of irresectability.

Patients and Methods

After protocol approval by our institutional review board (IRB). Patients with histologically confirmed colorectal carcinoma with unresectable CRLM and no extra-hepatic disease on cross-sectional imaging performed within 6 weeks of enrollment were approached for enrollment; informed consent was obtained from every patient. Irresectability was determined by two hepatobiliary surgeons and one radiologist and defined as: technical (a margin-negative resection requires resection of three hepatic veins, both portal veins, or the retro-hepatic vena cava; or, a resection that leaves fewer than 2 adequately perfused and drained segments), or biological (>6 metastases in a single lobe, with one lesion >5cm; or 6 bilobar metastases). While there is no standard definition of biological irresectability, the criteria given represent patients with aggressive biology and a very high risk of recurrence.

Exclusion criteria included prior treatment of CRLM with resection, thermo-ablation or radiation, inadequate end-organ function or Karnofsky performance-score <60%.

Pretreatment evaluation included contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, CT-angiogram to determine arterial anatomy, ¹⁸F-fluorodeoxyglucose positron emission tomography, HAI pump placement,^{30,31} tissue biopsy, and normal perfusion-flow scan (^{99m}TcTechnetium-labeled macroaggregated albumin study -TcMAA) through the pump.

Chemotherapy regimens

Patients were assigned to receive best systemic chemotherapy in combination with HAI FUDR based on their prior chemotherapy history. Patients who had received 2 cycles of oxaliplatin and had no persistent neuropathy received intravenous systemic Oxaliplatin (85 mg/m²), Irinotecan (125mg/m²), and Bev (5mg/kg). Those patients with prior treatment including >2 cycles of oxaliplatin received systemic Irinotecan (150mg/m²) and 5-Flourouracil (2000 mg/m² –48 hours infusion), Leucovorin (400 mg/m²) and Bev. HAI FUDR was given at of 0.12 mg/kg/day × kg × pump volume/flow rate and Dex at 1 mg/day × pump volume/flow rate with heparin and saline. Both were delivered over a 14 day continuous infusion through the pump.²⁸ Patients started treatment at least 2 weeks after pump placement. Therapy was administered in a 4-week cycle. HAI therapy was started on day 1 of each cycle, and the pump was emptied and filled with heparin (30000 units) and normal saline on day 15. Systemic chemotherapy was administered on day 1 and day 15 of each cycle.

Toxicity evaluation

All toxicities were rated by the NCI Common Terminology Criteria for Adverse Events (v 3.0).³² Patients were evaluated at least every 2 weeks during treatment. Evaluation included physical examination, complete blood count, complete metabolic panel and carcinoembryonic antigen. Biliary toxicity was graded as previously reported.^{28,33}

Study design and statistical analysis

This is a prospective, non-randomized, single-institution Phase-II trial registered in clinicaltrials.gov (Registration # NCT00492999). The primary end-point was resectability rate. Resectability assessment was made after the fourth cycle and then every 2 cycles. Response was evaluated according to WHO criteria.³⁴ Technically unresectable patients with sufficient response to allow complete resection with adequate future liver remnant proceeded to laparotomy for potential resection. Biologically unresectable patients with radiologic response or stable disease after 4 cycles of chemotherapy were taken to resection if technically feasible.

At the time of trial design, the reported conversion rates were approximately 15%.^{9–11,13} A sample size of 49 patients was estimated to provide 90% power (type-I error: 10%) to detect an increase in conversion rate from 15 to 30%. Although our prior retrospective review suggested a conversion rate of 47% we wanted this trial to be powered to at least detect a

doubling of the historical rate. Secondary endpoints included overall survival (OS), progression-free survival (PFS), RR and tolerability and safety.

OS, PFS, and time to hepatic progression (THP) were measured from the start of HAI therapy and estimated by Kaplan-Meier methods. In patients who underwent resection, progression was defined as the development of any new site of disease. A Cox proportional-hazards model was used to evaluate the association between conversion and survival outcomes, treating surgery as time-dependent covariate. The models were adjusted for clinical-risk-score (CRS) as a binary variable (high [CRS = 3, 4, 5] *versus* low [CRS = 0, 1, 2]) or other variables significantly associated with outcomes on univariate analysis ($P<0.10$).³⁵

To compare and graphically display the survival outcomes of patients that underwent resection versus those that did not undergo resection we used a landmark analysis using conversion to resection at 12 months of treatment as a pre-defined landmark time. Patients who did not have 12-months follow-up were excluded from the landmark analysis. The landmark analysis is an effective approach of removing the bias that exists in this type of analysis in which survival outcomes are compared among patients defined by other outcome (conversion to resection).³⁶ Correlation between clinical-pathologic characteristics and resection was examined using Fisher's exact test for categorical variables or Wilcoxon Rank-Sum test for continuous variables. All analyses were performed using SAS statistical software (Cary, NC, V9.2).

Results

Patient and Treatment Characteristics

A total of 102 patients with unresectable CRLM were assessed for eligibility between July 2007 and November 2010. Of these, 53 were not included in the protocol (1 myocardial infarction; 2 comorbid medical issues; 34 had extra-hepatic disease; 1 extrahepatic perfusion after pump placement; 2 jaundiced after surgery; 1 no tumor on path report; 1 FUDR started early; 1 patient refused; 1 peritoneal hematoma; 8 resected; 1 signed to another protocol). Forty-nine patients were enrolled. General demographics and presentation characteristics are detailed in Table 1

Toxicity

Details of chemotherapy related major toxicity are summarized in Table 2. The overall grade 3/4 toxicity rate was 41% (20/49). The first 24 patients accrued to the protocol received Bev and experienced an unexpectedly high rate of biliary toxicity with 3 patients requiring biliary stents. Based on these and additional data from other clinical trials that demonstrated increased biliary toxicity related to the addition of Bev to HAI FUDR,^{33,37,38} Bev was removed from the treatment after authorization from the IRB and protocol amendment. The subsequent 25 patients enrolled had a 28% rate of grade 3/4 toxicity and a significantly better biliary toxicity profile. Seven patients (14%) experienced a grade 1 or 2 complication associated with pump placement.

Most patients (32/49, 65%) received protocol treatment as either second (21/32) or third-line (11/32) therapy. Twenty-nine patients (59%) received systemic Irinotecan and 5FU/LV and 20 patients received systemic Oxaliplatin and Irinotecan. By three months of treatment, patients had received a median of 67% of the planned dose of HAI FUDR (range 59 – 83%), 88% of Oxaliplatin (range 80 – 100%), and 86% of Irinotecan (range 80 – 100%). By six months the median percentage of the planned doses were 42% (range 33 – 50%), 59% (range 49 – 85%) and 67% (range 55 – 83%), respectively.

Response and conversion to resection

The overall RR was 76% with 36 partial (PR) and 1 complete response (CR). Chemotherapy-naïve patients had a RR of 82% (14/17), one being a CR. In previously treated patients the RR was 72% (23/32). Patients with and without Bev treatment had similar RR (75% vs. 76%; *P*: 1.0). Large volume responses were common (Figure 1).

Twenty-three (47%) patients converted to resection at a median of 6 months from treatment initiation (range 3 – 22). Table 1 compares the characteristics of these patients with those who could not undergo resection. Two of the three biologically unresectable patients in the cohort underwent resection after a PR (one as a two-stage procedure). The third patient experienced progression of disease and was thus not considered a candidate for resection. Most patients (17/23) underwent formal anatomic resections (2 or more contiguous segments) accompanied by contralateral wedge resections and/or ablations. The remaining six patients underwent multiple, bilateral wedge resections or segmentectomies, in combination with ablation. Altogether, sixteen patients underwent concurrent ablation. Six patients underwent preoperative portal vein embolization. One patient had concurrent extra-hepatic disease (celiac lymph-node) resected at the time of liver resection. Five patients underwent a two-stage resection. Four additional patients underwent the first of a planned two-stage resection that were not completed due to progression of disease; these patients were not considered as resected. Fifteen of 23 specimens showed a significant pathologic response to chemotherapy (75%); 3 of which were pathologic CRs. Five resected patients (22%) had positive margins on pathologic examination.

Eight patients (35%) experienced a complication after resection, only one (4%) being grade 3 (a postoperative biloma requiring percutaneous drainage). There were no 90-day post-operative deaths.

Survival

The median follow up time was 38 months. Median OS was 38 months (95% CI: 28–not reached) (Figure 2A). Median survival for chemo-naïve patients has not been reached (95% CI: 28 months–NR) while previously treated patients had a median OS of 32 months (95% CI: 16–NR); *p* = 0.08. One and three-year OS for chemo-naïve patients was 94% (95% CI: 65–99) and 75% (95% CI: 46–90) versus 91% (95% CI: 74–97) and 44% (95% CI: 26–61) for previously treated patients (Figure 2A). Conversion to resection was the only factor associated with prolonged OS on univariate and multivariate analysis adjusting for CRS. Table 3.

The median PFS was 13 months (95% CI: 7–16). PFS for chemo-naïve and previously-treated patients was 20 (95% CI 6–26) and 10 (95% CI: 6–15) months; $p=0.08$ (Figure 2B). Two patients coded as progression ultimately came to resection; one with nodal disease resected after prolonged observation and one with a new liver lesion on imaging felt to be progression but ultimately proven to be benign fatty infiltration. Conversion to resection remained an independent predictor of prolonged PFS in multivariate model after adjusting for prior chemotherapy, CRS, and percent liver involvement (HR: 0.31 [95%CI: 0.15–0.62], $P: <0.001$). Table 3

Landmark analysis

Twenty patients underwent resection by the pre-specified Landmark time. These patients had longer OS compared to those who did not undergo resection (3-year OS: 80% vs. 26% - Figure 3A). There was no difference in PFS as seen in Figure 3B (median PFS: 8 months for both groups) or THP (median THP: 33 vs. 27 months; Figure 3C) between resected and unresected patients. Follow up time was 27 months (IQR: 24–40) and 17 months (IQR: 14–42) for resected and unresected patients respectively.

Post-resection recurrence, salvage procedures and long-term disease free survival

Of the 23 resected patients, 6 remain free of recurrence (1 died of unrelated reasons) at a median follow-up since resection of 28 months (range: 12–61). Of the remaining 17 patients that recurred after resection, 8 underwent complete resection and/or ablation of their liver-only ($n=7$) or lung-only ($n=1$) recurrences. Of these 8 patients, 4 remain NED at a median follow up of 5 months (range: 3 – 21 months) from the salvage procedure. One additional patient remains free of disease at 57 months after a radiologic CR without resection. In total, 10 of 49 (20%) patients are currently NED at a median follow up of 39 months (32–65).

Discussion

In well selected patients, complete resection of CRLM is associated with long-term survival. Untreated patients typically survive less than 1 year,^{3,5} while treatment with modern systemic chemotherapy is associated with a median survival of approximately 2 years but is rarely, if ever, curative. In a recent trial comparing systemic chemotherapy to thermal ablation for CRLM the systemic chemotherapy arm had a reported median survival of 40 months. While, this appears to be an improvement in outcomes, this reported survival is likely related to selection (patients had to have less than 10 tumors, no tumor greater than 4cm and no prior failure of chemotherapy) and the fact that 10% of these patients ultimately underwent resection.³⁹ For those patients on second line therapy, survival is usually less than 15 months. In patients with unresectable CRLM, a multidisciplinary approach combining chemotherapy to reduce tumor burden and a proactive approach to resection has been associated with long-term survival similar to that of patients with initially resectable disease.^{9,40,41} Conversion to complete resection is therefore a reasonable goal of treatment.

Resection of unresectable CRLM after down-staging with systemic chemotherapy has been reported in retrospective series.^{9,13,40,42} These studies report resection rates between 12 and 38%. While these data provide evidence that this strategy can be effective, limitations

inherent to retrospective studies temper the conclusions that can be drawn from those reports. Definitions of what constitutes unresectable disease are highly variable and were generally not pre-specified. Furthermore, the true denominator of patients with unresectable disease is often unclear or not reported. Therefore, the conversion rate may be inaccurate and overestimated.

In a recent study, 111 patients with unresectable CRLM were randomized to receive FOLFOX or FOLFIRI in addition to cetuximab. This study had prespecified criteria for irresectability, however, upon review of preoperative images by a panel of 7 surgeons, 32% of the patients enrolled were judged to be resectable at presentation. This raises obvious questions about the reported conversion rate of 46%.⁴¹ Another prospective phase-II trial evaluating irinotecan and 5FU/LV reported conversion to complete resection in 33% of patients; however, pre-treated patients were excluded.^{11,43} Modern prospective trials evaluating first-line systemic chemotherapy in unresectable CRLM have demonstrated RR between 47 and 68% and conversion to complete resection between 24–34%, which may be higher with the addition of biologic agents.^{11,15,44} However, RR in the second or third-line setting range between 6–32%, with median OS between 10–20 months.^{45,46}

The use of HAI chemotherapy to convert patients with unresectable CRLM to complete resection has also been reported. In 2002, Clavien et al. reported a pilot study using HAI for unresectable liver tumors.⁴⁷ Twenty-three patients with unresectable CRLM were treated with HAI FUDR and no additional systemic treatment. Response to therapy allowed resection in 6 patients (26%). Two prior phase-I trials reported that combination HAI and systemic Oxaliplatin and Irinotecan were well tolerated with an acceptable toxicity profile. The RR in these patients was 92% despite half of them being previously treated. Median survival from the start of chemotherapy was 51 and 35 months for chemotherapy-naïve and pre-treated patients, respectively. Furthermore, in a separate retrospective analysis of these trials, it was reported that 47% of patients experienced sufficient response to allow complete resection.^{27,28}

We designed the present prospective Phase-II trial specifically to evaluate the rate of conversion to resection in patients with unresectable CRLM treated with combination HAI and systemic chemotherapy. The trial was powered to detect an increase in conversion to resection from 15 to 30% based on current data at the time of design. This was felt to represent approximately a doubling of the conversion rate reported with systemic chemotherapy. While the power analysis is necessarily based on now dated references, this is a limitation of any prospectively designed, executed and reported trial. Furthermore, conversion to resection rates with current chemotherapy regimens are not significantly different. While the initial chemotherapy was planned to be combined with Bev, the biliary toxicity of this combination (see below) did not allow half the patient cohort to receive the Bev. Irresectability was prospectively defined and previously treated patients were allowed in the trial. Combination HAI and systemic therapy resulted in very high response rates in both previously treated (72%) and chemotherapy-naïve patients (82%); overall 8% CR (4 patients). The primary endpoint of the study (conversion to resection) was achieved with 47% of patients undergoing complete resection. Among the whole cohort, OS was 38 months, and one and 3-year survival rates were 92% and 55%, respectively. Of note, chemo-

naïve patients had OS rates of 94% and 75% at 1 and 3 years, respectively. These results are encouraging, especially considering the high rate of previously treated patients, the large bulk of disease, oncologic adverse features that most patients exhibited and that 94% of patients had technically unresectable disease.

The combination regimens used in this trial were generally well tolerated. The rate of grade 3/4 toxicity rate was 41%, the most common event being grade 3–4 diarrhea, and elevation of liver function tests. Major biliary toxicity was experienced by 13% of patients who received Bev prompting its removal from the protocol. In our experience the rate of biliary toxicity after HAI chemotherapy with FUDR is low (5.5%) and has been felt to occur in relation to the high concentration of chemotherapy in the arterial vessels feeding the bile duct.⁴⁸ We have also observed an increase in biliary toxicity when combining Bev and HAI FUDR in other protocols³⁷ and do not recommend the use of this combination. Although unproven, it is plausible that the anti-angiogenic effect of Bev has an impact on biliary arterial capillaries leading to ischemia and to an increased susceptibility to HAI-related biliary sclerosis. This underscores the importance of close monitoring of liver function tests and dose adjustments in patients receiving HAI therapy. Moreover, the surgical morbidity observed (35% - with only one major complication) compares favorably with our previously published experience.^{2,49}

Although this trial was not designed to evaluate survival differences between resected and unresected patients, we performed a landmark analysis to evaluate this issue. At the landmark time of 12 months after initiation of HAI therapy, 20 patients had undergone resection. Median survival was significantly better in these patients undergoing resection (3-year OS: 80% vs. 26%). Despite similar PFS and a 24% 1-year RFS, it is important to note that 20% of patients (10/49) were rendered disease-free with resection after initial progression (2 patients) or with salvage resection and/or ablation after recurrence (8 patients); and 39% of the patients who underwent resection are NED at the last follow up. This underscores the idea that these (highly selected) patients may be rendered disease-free with resection, and despite a very high risk of recurrence, their survival is still positively impacted by the possibility of salvage. Although there is insufficient follow-up time, natural history data⁵⁰ suggests that these patients with long-term disease-free survival may be cured. Importantly, despite apparently longer follow up time in the resected group, fewer events (deaths) are observed in this group; this again underscores the positive impact of resection on survival seen in the multivariable Cox regression.

The results of this trial may be difficult to extrapolate to the general population of patients with unresectable CRLM. The enrolled patients represent a unique population of relatively young patients with good functional status that present with extensive and heavily pretreated disease. Furthermore, conversion to resection is a somewhat subjective endpoint. While this trial clearly defines resectability and what must occur in order to become resectable, these definitions and related decisions reflect the bias of institutional practices and may not be reflective of practices at other institutions. Nonetheless, this prospective trial demonstrates the possible outcomes with a combination of HAI and systemic chemotherapy and resection whenever possible. While the encouraging survival may be as much related to selection as it is to the treatment regimen, the rate of long-term disease-free survival, with or without

salvage therapies after resection, is an indisputable outcome that rarely occurs with systemic chemotherapy alone.

In conclusion, the results from this phase-II clinical trial show that selected patients with strictly defined unresectable CRLM, despite pre-treatment with systemic chemotherapy and unfavorable oncologic characteristics can experience enough response after combination treatment with HAI and systemic therapy to become resectable. Despite high recurrence rates, our findings show that salvage therapy is feasible and a significant proportion of patients remain free-of-disease after prolonged follow up. A role for HAI chemotherapy in unresectable CRLM is supported by our findings; however, randomized studies are needed to further define this role in comparison with systemic chemotherapy. Furthermore, these findings cannot be attributable to the use of Bev due to its early removal from the trial design related to an unanticipated high toxicity profile.

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Figure 1.

Waterfall plot illustrating the percentage decrease in tumor size after treatment with hepatic arterial infusion of floxuridine/dexamethasone + best systemic therapy. Blue bars represent patients who had not received prior systemic chemotherapy. Dashed line separates responders and non-responders by WHO criteria

Figure 2. Overall (A) and progression free (B) survival in 49 patients treated with HAI and systemic chemotherapy. Survival was calculated since treatment start. Graphs depict all patients (green line) and stratified by prior therapy (blue: chemo naïve; red: previously treated).

Figure 3.

Landmark analysis. Time zero means 12 months from start of treatment. (A) Overall survival- 4 patients without 12 months follow up were excluded. $P=0.005$; (B) Progression-free survival-23 patients without 12 months follow up were excluded. $P=0.60$; (c) Time to hepatic progression- 18 patients without 12 months follow up were excluded. $P=0.96$

Table 1

Patient Characteristics and comparison of resected and non-resected cases

	All patients		No resection		Resection		P - value
	N	%	n (%)	n (%)			
Total	49	100	26	23			
Age							
Median (IQR)	56 (48 – 64)		53 (45 – 64)	59 (52 – 63)		0.67	
Gender							
Male	29	49	15 (58)	14 (61)		0.94	
Synchronous disease							
Yes	46	94	25 (96%)	21 (91%)		0.89	
Number of liver tumors							
Median (IQR)	14 (7 – 23)		17 (10–27)	9 (6–15)		0.13	
Prior Chemotherapy							
Yes	32	65	19 (73%)	13 (57%)		0.36	
BEV							
Yes	24	49	15 (58%)	9 (39%)		0.29	
Clinical Risk Score							
3,4,5	44	90	24 (92%)	20 (87%)		0.91	
Size of largest tumor							
>5cm	16	33	10 (38%)	6 (26%)		0.55	
LN positivity							
Yes	39	80	22 (85%)	17 (74%)		0.55	
CEA>200							
Yes	15	31	10 (38%)	5 (22%)		0.37	
Disease free interval							
<12 months	46	94	25 (96%)	21 (91%)		0.89	
Criteria for irresectability							
Biological	3	6	1 (4%)	2 (8%)		0.91	
Technical ^a	46	94	25 (96%)	21 (92%)		0.98	
Response Rate							

All patients		No resection		Resection	P - value
		%	n (%)	n (%)	
WHO PR or CR	n (%)	76	16 (61%)	21 (91%)	0.04

IQR: Interquartile range; BEV: bevacizumab; LN: Lymph node; CEA: Carcinoembryonic antigen; WHO: world health organization response criteria.

^aIncludes irresectability due to bilateral vascular involvement (R0 resection would require resection of bilateral portal veins, inferior vena cava and/or 3 hepatic veins), or an functional liver remnant < 2 segments.

Table 2

Toxicity profile stratified by Bevacizumab administration

Toxicity Event	Bev (n=24)		No Bev (n=25)		Total (n=49)	
	Number	%	Number	%	Number	%
Gr 3/4 Diarrhea	9	38%	5	20%	14	29%
Gr 3 Alk	8	33%	2	8%	10	20%
Gr 3 AST	5	21%	3	12%	8	16%
Gr 3 Abdominal pain	5	21%	1	4%	6	12%
Gr 3/4 Neuro	4	17%	2	8%	6	12%
Biliary Stents	3	13%	1	4%	4	8%
Gr 3 Bilirubin	2	8%	0	0%	2	4%
Gr 4 Bilirubin	1	4%	1	4%	2	4%
Gr 3 WBC	1	4%	0	0%	1	2%
Gr 2 HGB	1	4%	1	4%	2	4%
Gr 3 Nausea	1	4%	1	4%	2	4%
Gr 3 Vomiting	1	4%	2	8%	3	6%
Gr 3 Mucositis	1	4%	0	0%	1	2%
Gr 4 Platelets	0	0%	1	4%	1	2%

Alk: Alkaline phosphatase; AST: aspartate aminotransferase

Table 3

Cox regression model for overall and progression-free survival

Clinical Variables	Overall Survival				Progression-free survival			
	HR	95%CI	P - value	HR	95%CI	P - value	HR	95%CI
Age at diagnosis			0.32			0.51		
>=60	0.64	0.26–1.55		0.81	0.44–1.50			
<60	1			1				
Tumor involvement	1.02	0.95–1.08	0.62	1.01	0.97–1.05	0.55		
Synchronous tumor						0.83		
Yes	1.4	0.18–10.3	0.84	0.88	0.27–2.87			
Prior Chemotherapy			0.08			0.08		0.03
Yes	2.40	0.88–6.40		2.2	0.83–6.23		2.1	1.06–4.32
Liver involvement (%)	1.02	0.98–1.06	0.27	1.03	0.99–1.05	0.06	1.03	0.98–1.06
Clinical Risk Score^a								
3,4,5	1.12	0.26–4.80	0.93	0.8	0.18–3.53	0.77	0.92	0.31–2.69
Largest tumor >=5cm								
Yes	1.14	0.48–2.68	0.8	1.42	0.75–2.64	0.3		
CEA >200								
Yes	1.2	0.50–2.84	0.7	1.02	0.53–1.97	0.9		
LN positivity								
Positive	3.21	0.75–13.7	0.1	1.7	0.81–3.54	0.2		
Disease free interval								
<12mths	1.39	0.18–10.3	0.7	0.88	0.27–2.87	0.8		
BEV								
Yes	1.08	0.46–2.49	0.9	0.8	0.44–1.44	0.5		
Conversion to surgery^b								
Yes	0.17	0.05–0.52	0.02	0.16	0.05–0.49	0.001	0.26	0.15–0.62
						<0.0001	0.31	0.15–0.62
								0.001

^a The individual variables in the clinical risk score (Largest tumor > 5 cms, CEA >200, LN positivity, and disease free interval) were not included in the multivariate regression. Only the total score as a binary variable (i.e. high [CRS: 3,4,5] versus low [CRS: 1,2]) was included.

^b Resection was coded as time dependent covariate in the regression model