Review: Incidence and clinical significance of Bevacizumab-related non-surgical and surgical serious adverse events in metastatic colorectal cancer

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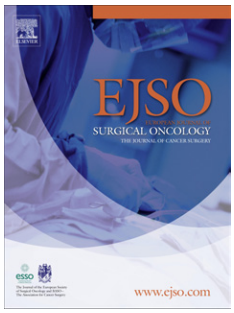

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Title page: **Review:**

Incidence and clinical significance of Bevacizumab-related non-surgical and surgical serious adverse events in metastatic colorectal cancer.

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Abstract:

Objective and Background: This review describes the extent, frequency and clinical importance of Bevacizumab(BV)-related serious adverse events (SAE) after surgery, during or after chemotherapy with BV in patients with metastatic colorectal cancer (mCRC).

Methods: Detailed PubMed search in november 2009.

Results: Addition of BV to first- or second-line chemotherapy in patients with mCRC results in a statistically significant benefit in OS, PFS and RR.

Addition of BV to chemotherapy causes no clinically relevant aggravation of SAE and seems safe with the primary tumor still in situ. The risk of emergency surgery due to BV-related SAE is estimated 2.0%.

SAE rate is low if a time to surgery of 5-6 weeks is respected. The majority of SAE are wound healing complications. Bleeding and GI perforation occur infrequently, even following major surgery after BV-treatment. Major surgery during the course of BV-treatment results in an SAE rate of 1.3-2.7%. Postoperatively, a period of minimally 28 days should be respected before starting BV.

Conclusion: Reported rates of BV-related SAE in relationship to surgery are low.

Keywords:

Metastatic colorectal cancer, bevacizumab, complications, surgical, non-surgical

Abbreviations:

Vascular endothelial growth factor (VEGF), Bevacizumab (BV), VEGF receptor (VEGFR), adverse events (AE), serious adverse events (SAE),arterial hypertension (AHT), gastrointestinal (GI), wound healing complications (WHC), arterial thromboembolic events (ATE), venous thromboembolic events (VTE), time to surgery (TTS), colorectal cancer (CRC), metastatic CRC (mCRC), overall survival (OS), progression-free survival (PFS), response rate (RR), randomized controlled trial (RCT), 5-fluorouracil/leucovorin (5FU/LV), Memorial Sloan Kettering Cancer Center (MSKCC)

Review:

Incidence and clinical significance of Bevacizumab-related non-surgical and surgical serious adverse events in metastatic colorectal cancer.

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Introduction

Angiogenesis is the formation of new blood vessels by remodeling and expansion of primary vessels, which is crucial for tumor growth beyond 1-2mm and for metastasis. Tumoral angiogenesis is the result of complex molecular mechanisms and appears to be highly related to oxygen deprivation. Vascular endothelial growth factor (VEGF) is a glycoprotein that induces neovascularization and has an increased expression in tumor cells. Angiogenesis of tumor vasculature is fenestrated, chaotic and abnormal, which creates abnormal blood vessels and impairs effective delivery of chemotherapeutic agents to the targeted cancer cells[1-3].

Bevacizumab (BV) is a humanized monoclonal antibody that neutralizes the ability of all active VEGF-isoforms to bind to the VEGF receptor (VEGFR) on the surface of endothelial cells. It has 2 potentially cytostatic effects: prevention of neovascularization and normalization of immature and abnormal blood vessels[1,4,5]. This is assumed to retard the shedding of metastatic cells in the circulation and improve the delivery of therapeutic agents in tumors[6]. Pharmacodynamic data on BV suggest that combination with cytotoxic chemotherapy enhances its anti-tumor activity[1].

On the other hand, VEGF has critical role in wound healing, liver regeneration and endothelial integrity. Therefore, one can expect an anti-VEGF agent, such as BV, to cause mechanism-related serious adverse events (SAE) due to the reduction of VEGF availability[5]. The most frequently described side effects are arterial hypertension (AHT), gastrointestinal (GI) perforations, wound healing complications

(WHC), serious bleeding, arterial and venous thromboembolic events (ATE and VTE), renal toxicity and influences on liver parenchyma[5,7-13]. Pharmacokinetic studies show that BV has a half-life of 20 days [range 11-50 days]. Consequently, BV-effects may persist despite discontinuation before surgery, but the time for dissipation of BV's pharmacologic effects after the last dose has not been established. A dose of 5mg/kg every 2 weeks is accepted to be the most effective dose of BV. Waiting for two half-lives (i.e. ±6 weeks) would leave the equivalence of a dose of 1.25mg/kg in the circulation. This is far above the BV level that removes free VEGF from the circulation[14-16]. Hence, the time to surgery (TTS) that should be respected after discontinuation of BV has not been clearly defined yet. Recommendations vary from a TTS of 5-6 weeks[1,7,17] to a more careful 6-8 week interval[16]. For postoperative initiation of BV a period of 28 days after surgery and a fully healed surgical incision are recommended, because of possible impairment of wound healing under BV[16-18].

The aim of this paper is to review currently available literature, describing the actual extent, frequency and clinical importance of BV-related SAE after minor and major surgery, during or after systemic chemotherapy with BV, in patients with metastatic colorectal cancer (mCRC).

Methods

A detailed PubMed search was performed in september 2010, using the following keywords: angiogenesis, angiogenesis-inhibitors, VEGF, anti-VEGF, bevacizumab, Avastin, surgery, complications, adverse events, metastatic colorectal cancer, wound healing, bleeding, hemorrhage, gastrointestinal perforation, thrombo-embolism. The search was limited to articles published in the English language and the eldest publication extracted dates from February 2001.

Results

Overall Survival, Progression-Free Survival and Response Rate [Table 1]

Table 1 gives an overview of data on overall survival (OS), progression-free survival (PFS) and response rate (RR) reported by 7 randomized controlled trials

(RCTs)[19-25,31], 4 prospective[8,26-28] and 3 retrospective studies[11,29,30]. A recent Cochrane Database systematic review by Wagner et al., including 5 randomized trials (>3000 patients)[19,22,23,25,31], concluded BV prolongs both PFS and OS in patients with mCRC. The effect on PFS shows significant heterogeneity, which is probably attributable to differences in the treatment effect of BV in combinations with different "chemotherapy backbones" (i.e. different combinations of 5FU/LV, oxaliplatin, irinotecan). Furthermore, an absolute increase in tumor response of approximately 3% was found in favor of the patients treated with BV[2].

Non-surgical BV-related Serious Adverse Events

Prospective data (observational trials and RCTs)

Table 2 summarizes the serious adverse events (SAE, i.e. grade 3-5 adverse events) assumed to be related to BV-based chemotherapy, as reported by 6 RCT, 2 prospective observational trials and one pooled analysis of 2 RCT[19-28]. The authors agree that most BV-related adverse events (AE) are mild to moderate in severity and manageable using standard therapies. The First BEAT study reported grade 5 toxicity in 2% of patients, including hemorrhage (<0.5%), cardiac disorders (<0.5%), respiratory disorders (<0.5%), venous embolism (1%) and GI perforation (0.4%). An intention-to-treat-based analysis showed a 3% 60-day mortality[27]. The review by Wagner et al. showed no significant differences for treatment-related deaths and 60-day mortality with or without BV[2]. However, the number of treatment interruptions due to AE was significantly higher under chemotherapy with BV than without (21% versus 15%)[2]. The majority of trials attributed the most significant increase in toxicity to a significantly higher incidence of arterial hypertension (AHT) [Table 2]. Many trials also reported an increase in ATE [Table 2]. According to the analysis by Wagner et al. the increase in grade 3-4 AHT and ATE should be rated as statistically significant[2]. Bleeding as a SAE was reported from 0 to 5% in patients under BV-based treatment [Table 2]. In the ECOG study E3200 the incidence of hemorrhage was statistically higher for patients under second-line chemotherapy with BV (p=0.011)[22]. This was confirmed by the review of Wagner et al., whereas a non-significant increased incidence of bleeding was found under BV in first-line chemotherapy[2]. GI perforation was defined by Kabbinavar et al. as all events reported as GI abscess, perforation

and fistula of any grade unrelated to surgery[20]. A rate of "spontaneous" GI perforations under BV of up to 3% was recorded [Table 2]. An extensive meta-analysis by Hapani et al. reported an incidence of GI perforation under BV treatment of <1%, resulting in a mortality of 22%[32]. Patients under BV-treatment had a significantly increased risk of GI perforation, with a positive correlation with higher doses of BV (5mg/kg versus 2.5mg/kg per week) and colorectal cancer (CRC)[32]. In general, most authors agreed the addition of BV to chemotherapy caused no clinically relevant aggravation of chemotherapy-related SAE. Patients aged ≥65 years didn't appear to have greater risk with BV-treatment than younger patients[20,28], except for a relatively higher proportion of ATE in patients ≥75 years[2,28]. Furthermore, despite more ECOG PS score >1 and more comorbidities in the BRiTE study, the SAE rate was not substantially different from other BV-treated RCT cohorts[28].

Risk for emergency surgery under BV-treatment?

Few papers specify the risk for emergency surgery that is due to SAE in patients under BV-treatment. Poultsides et al. retrospectively described that out of 233 patients who received up-front triple drug chemotherapy (with oxaliplatin or irinotecan) with or without BV 16 patients (7%) underwent emergent surgery under chemotherapy: 5 resections for perforations and 3 resections plus 8 diversions for primary tumor obstruction[30]. Only 2 of the 5 tumor perforations occurred under BV-treatment. For the obstructive events the number of patients under BV was not clearly specified. No intractable bleedings, necessitating surgical intervention, were reported. Two patients with primary tumor complications (<1%) died within 30 days of surgery. The authors didn't specify whether these patients were on BV-treatment, but they concluded that the risk of emergent intervention was not associated with the use of BV[30]. Of 529 patients under BV-based treatment in the ECOG study E3200 only 1 developed a grade 4 bleeding that required a hemostatic intervention and 6 events of bowel perforation were reported, 2 of which needed surgery and 2 cases were fatal[22]. In a multicenter trial of Kabbinavar et al. 2 of the 104 patients under BV-based treatment developed a bowel perforation (each associated with a colonic diverticulum). One patient died due to this complication. Nevertheless, SAE leading to death or study discontinuation were found to be similar with or without BV[23], which concurs with the analysis of Wagner et al[2].

Risks of BV-treatment if the primary tumor is still in situ?

In case of asymptomatic synchronous stage IV CRC, the rationale for immediate resection of the primary tumor would be the prevention of primary-related AE that might make urgent surgery under chemotherapy necessary, thus possibly increasing mortality. On the other hand, immediate resection of an asymptomatic primary might cause an important delay or even exclude some patients from chemotherapy[30]. Few trials report specifically on the incidence of major complications related to the primary tumor in synchronous stage IV CRC under BV-based therapy. The First BEAT study reported a GI perforation in 8 of 223 patients (4%) with unresected primary tumors: only 3 of them occurred at the primary tumor site[27]. In the BRiTE study GI perforation rate was 3% in patients with an intact primary versus almost 2% in case of a resected primary tumor[28]. Multivariate analysis rated this as an independent risk factor for GI perforation, but event numbers were low: only 9 out of 305 patients (3%) with an unresected primary tumor developed a GI perforation. Whether these perforations occurred at the primary tumor site, was not specified. Based on a literature search, Poultsides et al. concluded that virtually all BV-related perforations were observed in the first 3 months of treatment (mostly within the first month) and occurred throughout the entire GI tract, hardly ever involving the site of the primary tumor[22,25,30].

BV-related complications after surgery

RCT data [Table 3]

The pooled analysis by Scappaticci et al.[33] includes 1132 patients, who underwent 5FU/leucovorin- or Folfiri-based chemotherapy with or without BV in a phase II[23] and phase III RCT[25]. This population was analyzed in two groups: In group 1 chemotherapy (with or without BV) was started 28-60 days after surgery and complication rates were similarly low in both groups (around 1%). In group 2 patients underwent major or emergent surgery during chemotherapy with or without BV. The higher number of surgical procedures in BV-treated patients was not explained, but apparently there were more elective, non-cancer related procedures in this group. The difference in SAE incidence with or without BV (13% versus 3%) didn't reach statistical significance. Nevertheless, it might have clinical relevance, so careful monitoring of patients who need to undergo major surgery during BV-based

chemotherapy is recommended. The “major” surgical procedures in the pooled analysis by Scappaticci et al. are listed in Table 5B. The small number of events in this analysis made it impossible to draw definite conclusions on the appropriate timing of surgery following the last BV dose as well as the influence of comorbidity (e.g. diabetes, obesity, smoking) on healing processes[33]. The NSABP C-08 trial (National Surgical Adjuvant Breast and Bowel Project) compared Folfox with or without BV in the adjuvant setting for stage II and III CRC. In this study BV increased the risk of wound healing complications (WHC), even if it was initiated 6 weeks from the time of surgery. Furthermore, it was suggested that extended use of BV can increase the long-term risk of WHC for up to 6 months after its cessation[18,34].

Prospective observational data [Table 4]

In the First BEAT study almost 12% of patients underwent surgery with curative intent “during trial participation”, of whom 64% (145 patients) underwent hepatectomy [Table 5A]. Bleeding was reported as an SAE in almost 3% and WHC in 2.0%[27]. In the BRiTE study almost 27% patients underwent surgery within 90 days of the last BV dose, of whom 30% (175 patients) underwent major abdominal surgery and 17% (88 patients) underwent hepatectomy. The incidence of serious WHC was 4.4%. The absolute number of severe WHC appeared higher after major than after minor surgery: 6% of abdominal procedures and 6% of hepatectomies developed severe WHC versus 3% for minor surgical procedures[28] [Table 5B]. A subanalysis of the time to surgery (TTS) was performed [Table 5B], but no multivariate analysis was performed for WHC because event numbers were low. Concerning severe bleeding, a multivariate analysis couldn’t identify significant risk factors, not even antiplatelet therapy or anticoagulation[28]. This concurs with a trial of Saltz et al., who found bleeding events to be similar for BV-based chemotherapy with and without concurrent anticoagulation therapy[19]. Unfortunately, the BRiTE study and the First BEAT trial didn’t clearly specify the number of severe bleeding events that occurred postoperatively. Gruenberger et al. prospectively reported on 52 liver resections 5 weeks after BV[35]: Thirty-six percent of patients underwent a major hepatectomy (i.e. resection of ≥3 liver segments) [Table 5A]. Eleven postoperative SAE were recorded: 1 bowel perforation (for which reoperation was needed), 1 anastomotic leak, 1 wound hematoma, 1 wound infection, 3 cases of sepsis and 1 bile leak. There were no severe bleeding events. Twenty-one percent of patients underwent

synchronous resection of liver and primary tumor [Table 5A], resulting in similar peri- and postoperative complication rates as in patients undergoing only hepatectomy. Concerning liver function and regeneration, Gruenberger et al. reported normal findings in 51 patients (98%)[26]. This concurs with observations from MD Anderson[11] and a retrospective analysis by Klinger et al[8], which suggests a reduced incidence and severity of oxaliplatin-related sinusoidal dilatation in patients under chemotherapy with BV. Finally, 2 phase I studies by Willett et al. included a very small number of patients who all underwent major surgery after BV-based chemotherapy. Reported complications were low[6,36] [Table 5B].

Retrospective data

Zawacki et al. performed the only study focusing purely on minor surgery under BV-based chemotherapy [Table 5C]. They analyzed WHC as a SAE under BV-treatment with variable doses before or after placement of a venous access port. All 6 dehiscences occured under BV-treatment. Despite the very small number of events statistical analysis was performed and the authors concluded that patients receiving BV within 10 days of port placement had a higher incidence of wound dehiscence[37]. A study from MD Anderson focused on hepatic surgery after chemotherapy with or without BV: 30% of patients underwent major hepatectomy[38] [Table 5A]. Median time between discontinuation of BV and surgery was 58 days [range 31-117]. No significant association was found between use of BV and postoperative complication rate (49% with vs. 43% without BV). The time interval from discontinuation of BV to surgery was not associated with an increased likelihood of developing complications[38]. Reddy et al. analyzed morbidity of hepatectomy after irinotecan- or oxaliplatin-based chemotherapy with or without BV: 24% of patients underwent major hepatectomy and in 16% of patients synchronous extrahepatic procedures were performed[39] [Table 5A]. The differences in complications after chemotherapy with or without BV were all rated statistically insignificant. An analysis for TTS (≤ or >8 weeks) showed no significant differences for overall, severe and hepatic complications[39]. D'Angelica et al. studied the influence of BV-based chemotherapy within 12 weeks from hepatectomy: 27% of patients underwent major hepatectomy[40] [Table 5A]. Only 2 SAE (grade 3) were reported under BV: 1 subphrenic abscess and 1 groin abscess. Because of the heterogenous timing of BV administration (before, after or before and after surgery) and the low complication rate definitive conclusions

are difficult, but the perioperative complication profile was within the limits expected in any group of patients undergoing hepatectomy[40]. Finally, Bose et al. suggested that, although a period of 28 days is recommended for postoperative initiation of BV, the time point for the start of BV should be individualized in case of comorbidity (e.g. diabetes, peripheral vascular disease) or wound-healing issues, thus allowing more time for wound healing[16].

Discussion

The BV-related SAE reported in literature are mild to moderate in severity and manageable using standard therapies. Furthermore, the incidence of SAE under BV-based chemotherapy is low: even very large, multicenter prospective and randomized controlled trials reported only very small numbers of SAE. In most trials the incidence of hemorrhage (2.0-3.0%), GI perforation (<1.0-2.0%) and ATE (1.0-2.0%) was higher under BV-based treatment, but overall the absolute number of patients affected remained very low. Also, BV-related grade 5 toxicity was rare. Thus, most authors agreed the addition of BV to chemotherapy caused no clinically relevant aggravation of chemotherapy-related SAE. Only few trials report specifically on the incidence of major complications related to the primary tumor in synchronous stage IV CRC under BV-based therapy. With the primary tumor still in situ during chemotherapy, BV-related GI perforations occur in about 3% of patients, but virtually all of these were observed in the first 3 months of treatment and occurred throughout the entire GI tract, hardly ever involving the primary tumor site. Thus, leaving the primary tumor in place during BV-treatment appears safe. Finally, the risk emergency surgery might be needed due to BV-related SAE, such as bleeding or perforation, is very low (estimated 2.0%).

The relation between postoperative SAE and BV-based chemotherapy can be divided in 3 groups: First, for patients undergoing surgery after BV discontinuation trials showed very low rates of SAE if a TTS of 5-6 weeks is respected. The majority of SAE reported are WHC. Bleeding and GI perforation occur infrequently. In most of these trials 30-40% of patients undergo major surgery, which suggests the low rate of SAE reported should be reliable. For minor surgery, WHC are the main issue, but rates are low if BV is discontinued within a 10 day period around the procedure.

Second, patients undergoing major or emergency surgery during BV-treatment seemed at higher risk (SAE 1.3-2.7% vs. 0.0%), but this was rated statistically insignificant. The reported numbers of SAE remained relatively small in this setting, but they could still be clinically relevant. Thus, close monitoring of patients undergoing surgery under BV is advisable. Third, for the start of BV-treatment after major surgery few data are available. Small rates of SAE were found, especially if a period of minimally 28 days after surgery is respected before starting BV. However, in case of comorbidity or wound-healing issues after surgery, the time point for starting BV should be individualized to allow more time for wound healing.

Conclusion

This review shows that even trials consisting of large patient populations report small numbers of SAE of BV-related SAE in relationship to surgery. This has 2 consequences: Small numbers of events make statistical analysis and definitive conclusions difficult, if not impossible. On the other hand, the fact that even large populations show low absolute numbers of BV-related SAE in any of the settings examined above, suggest that BV-based treatment causes few clinically significant problems even when surgical procedures are involved.

Conflict of interest statement:

The authors have no disclosures to make concerning financial and personal relationaships with other people or organizations that could inappropriately influence (bias) their work.

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Table 1: Therapy with BV: OS / PFS / RR / CR

	Ref.	Author *Trial* Journal	N +BV / total	Regimen	OS (m)	PFS (m)	ORR (%)	Complete response on pathology (%)
RCTs	[19]	Saltz *Amended NO16966 trial* JCO 2008	699/1400	Folfox / Capox +BV	21.3	9.4	47.0	-
					vs	vs	vs	
				Folfox / Capox -BV	19.9 (p=0.077)	8.0 (p<0.0023)	49.0 (p=0.31)	-
	[21]	Hochster *Amended TREE study* JCO 2008	213/360	ivFolfox / bolusFolfox / Capox +BV	23.7	9.9 / 8.3 / 10.3	45.7	-
					vs	vs	vs	
				ivFolfox / bolusFolfox / Capox -BV	18.2	8.7 / 6.9 / 5.9	29.3	-
	[22]	Giantonio *ECOG study E3200* JCO 2007	529/820	Folfox +BV	12.9	7.3	22.7	-
					vs	vs	vs	
				Folfox -BV	10.8	4.7	8.6	-
					vs	vs	vs	
				BV alone	10.2 (p=0.0011)	2.7 (p<0.0001)	3.3 (p<0.0001)	-
	[23]	Kabbinavar* JCO 2005	104/209	5FU/LV +BV	16.6	9.2	26.0	-
					vs	vs	vs	
				5FU/LV -BV	12.9 (p=0.16)	5.5 (p=0.0002)	15.2 (p=0.055)	-
	[24]	Kabbinavar JCO 2005	249/490	IFL +BV	17.9	8.7	34.1	-
				IFL -BV	14.6 (p=0.0081)	5.55 (p=0.0001)	24.5 (p=0.019)	-
	[25]	Hurwitz** N Engl J Med 2004	402/813	IFL +BV	20.3	10.6	44.8	-
					vs	vs	vs	
				IFL -BV	15.6 (p<0.001)	6.2 (p<0.001)	34.8 (p=0.220)	-
	[20]	Kabbinavar JCO 2009	218/439	5FU/LV or IFL +BV	19.3	9.2	34.4	-
					vs	vs	vs	
			Patients ≥ 65years (pooled analysis */**)	5FU/LV or IFL -BV	14.3 (p=0.006)	6.2 (p<0.0001)	29.0 (p=0.220)	-
Prospective trials	[27]	Van Cutsem *First BEAT study* Ann Oncol 2009	1914/1914	5FU-based chemotherapy +BV	22.7	10.8	-	-
	[28]	Kozloff *BRiTE study* The Oncologist 2009	1953/1953	"BV-containing therapy" (mainly 5FU-based)	22.9	9.9	-	-
	[26]	Gruenberger EJSO 2009	56/56	Capox +BV	-	-	-	8.9
	[8]	Klinger EJSO 2009	56/106	Capox +BV	-	-	-	8.9
								vs
				Capox or Folfox –BV	-	-	-	4.0
								(p=0.57)
Retrospective trials	[30]	Poultsides JCO 2009	112/233	Irino- or Oxali-based chemo +/-BV	18.0	-	-	14.5
	[11]	Ribero Cancer 2007	62/105 (285 nodules)	5FU/Oxaliplatin +BV	-	-	-	11.3
								vs
				5FU/Oxaliplatin +BV	-	-	-	11.6
								(p=0.59)
	[29]	Blazer JCO 2008	114/305	Irino- or Oxali-based chemo +BV	-	-	-	9.3
								vs
				Irino- or Oxali-based chemo +BV	-	-	-	9.2

Table 2: RCTs / Prospective trials: non-surgical BV-related SAE

	Ref.	Author *Trial* Journal	N +BV / total	Regimen	Non-surgical SAE (%)							
					Hemorrhage	GI perforation	ATE	VTE	AHT	Diarrhea	Leucopenia / neutropenia	Death (within 60d.)
RCTs	[19]	Saltz *Amended NO16966 trial* JCO 2008	699/1400	Folfox / Capox +BV	2.0	<1.0	2.0	8.0	4.0	-	-	2.0
				vs	vs	vs	vs	vs				vs
				Folfox / Capox -BV	1.0	2.0	1.0	5.0	1.0	-	-	1.6
	[21]	Hochster *Amended TREE study* JCO 2008	213/360	ivFolfox / bolusFolfox / Capox +BV	1.4	2.3	-	2.7	3.6	18.6	26.0	1.9
				vs			vs		vs	vs	vs	
				ivFolfox / bolusFolfox / Capox -BV	0.0	-	-	1.3	-	29.3	28.7	3.4
	[22]	Giantonio *ECOG study E3200* JCO 2007	529/820	Folfox +BV	3.4	0.6	0.9	3.4	6.2	-	-	5.0
				vs	vs	vs	vs	vs				vs
				Folfox -BV	0.4	0.0	0.4	2.5	1.8	-	-	4.0
				vs	vs	vs	vs	vs				vs
				BV alone	2.1 (p=0.011)	0.8	0.4 (p=0.62)	0.4 (p=0.62)	7.3 (p=0.008)	-	-	6.0
	[23]	Kabbinavar* JCO 2005	104/209	5FU/LV +BV	5.0	2.0	10.0	9.0	16.0	39.0	5.0	5.0
				vs	vs	vs	vs	vs	vs	vs	vs	
				5FU/LV -BV	3.0	0.0	5.0	11.0	3.0	40.0	14.0	13.5
	[24]	Kabbinavar JCO 2005	249/490	IFL +BV	5.0	1.0	5.0	10.0	16.0	37.0	5.0	-
				vs	vs	vs	vs	vs	vs	vs	vs	
				IFL -BV	2.0	0.0	3.0	9.0	3.0	34.0	19.0	-
	[25]	Hurwitz** N Engl J Med 2004	402/813	IFL +BV	3.1	1.5	19.4		11.0	32.4	37.0	4.9
				vs	vs	vs			vs	vs	vs	vs
				IFL -BV	2.5	0.0	16.2 (p=0.26)		2.3	24.7	31.1	3.0
	[20]	Kabbinavar JCO 2009	218/439 Patients ≥ 65years (pooled analysis */**)	5FU/LV or IFL +BV	4.8	2.9	7.6	14.9	13.8	38.6	30.0	6.7
				vs	vs	vs	vs	vs	vs	vs	vs	
				5FU/LV or IFL -BV	3.7	0.0	2.8	17.5	1.8	33.2	23.5	8.8
Prospective trials	[27]	Van Cutsem *First BEAT study* Ann Oncol 2009	1914/1914	5FU-based chemotherapy +BV	3.0	2.0	1.0	-	5.0	4.0	-	3.0
	[28]	Kozloff BRiTE study The Oncologist 2009	1953/1953	"BV-containing therapy" (mainly 5FU-based)	2.2	1.9	2.0	-	22.0	-	-	2.1
	[26]	Gruenberger EJSO 2009	56/56	Capox +BV	0.0	2.0	7.0		3.0	33.0	10.0	0.0

Tables 1 & 2:
p-values are mentioned if available
Abbreviations: ng: not given; p=NS: statistically not significant; N +BV/total = number of patients undergoing surgery during or after BV-based treatment over the total population

Table 3: RCT: post-surgery BV-related SAE

Ref.	Author Journal	N surgery +BV / total		Regimen	Post-surgery SAE (%)							
					GI perforation	Abd. fistula	Anastomotic dehiscence	Intra-abd. bleeding	Other Hemorrhages	Wound Healing	Infection	death
[33]	Scappaticci J Surg Oncol 2005	305/1132 (pooled analysis */**)	Group 1: Start BV 28-60d. AFTER surgery	5FU/LV or IFL +BV	0.9	-	-	0.4	-	-	-	-
					vs			vs				
				5FU/LV or IFL -BV	0.0	-	-	0.5	-	-	-	-
			Group 2: Major / emergency surgery DURING BV-treatment	5FU/LV or IFL +BV	2.7	2.7	1.3	1.3	1.3	1.3	2.7	2.7
					vs	vs	vs	vs	vs	vs	vs	vs
				5FU/LV or IFL -BV	0.0	0.0	3.4	0.0	0.0	0.0	0.0	3.4

Table 4: Prospective observational trials: post-surgery SAE

Ref.	Author *Trial* Journal	N surgery +BV / total	TTS	Regimen	Post-surgery SAE (%)						
					GI perforation	Abd. fistula	Anastomotic dehiscence	Hemorrhage	Wound healing	Wound infection	other
[27]	Van Cutsem *First BEAT study* Ann Oncol 2009	225/1914	"during trial participation"	5FU-based chemotherapy +BV	-	-	-	2.7	2.0	-	-
[28]	Kozloff *BRiTE* The Oncologist 2009	521/1953	"within 90 days" 0-2 weeks 2-4 weeks 4-6 weeks 6-8 weeks >8 weeks	"BV-containing therapy" (mainly 5FU-based)	-	-	-	-	4.4 9.7 3.2 3.0 5.9 2.2	1.5	-
[26]	Gruenberger JCO 2008	56/56	5 weeks	Capox +BV	2.0	-	2.0	0.0	4.0	2.0	Bile leak 2.0 Sepsis 6.0
[35]	Gruenberger JCO 2006	9	5 weeks	Capox +BV	-	-	-	0.0	0.0	11.1	0.0
[36]	Willett JCO 2005	5	7-9 weeks	5FU +BV + radiotherapy	20.0	0.0	0.0	0.0	0.0	0.0	20.0
[6]	Willett Nat Med 2004	6	7 weeks	5FU +BV + radiotherapy	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 5: Types of surgery vs postop.complications

Ref.	Author (center) Journal	N surgery +BV / total	Types of surgery	TTS	TpS	Post-surgery SAE (%)								
						Hepatic / biliary complications	GI perforation	Abd. Fistula	Anastomotic dehiscence	Hemorrhage	Wound Healing	Infection	other	Death
A. Liver surgery														
[27]	Van Cutsem *First BEAT* Ann Oncol 2009	225/1914	Curative hepatectomy 145	"during trial participation"	-	-	-	-	-	2.7	2.0	-	-	3.0
[38]	Kesmodel JCO 2008	81/125	Extended hepatectomy (≥5 segm) 17 Hemihepatectomy (3 or 4 segm) 30 Biseg/segmentectomy 12 Wedge resection 17 RFA only 5 RFA in addition to resection 20 Extrahepatic procedure 12	58 days range [31-117]	-	9.1 vs 9.1	- vs -	- -	1.2 vs 0.0	- -	2.5 vs 0.0	3.7 vs 0.0	12.3 vs 9.1	1.2 vs 2.3
[39]	Reddy J Am Coll Surg 2008	39/96	Extended hepatectomy 11 Hemihepatectomy 11 Other continuous 3-segmentectomy 1 Bisegmentectomy 12 Unisegmentectomy 1 Wedge resection 3 Synchronous hepatic & extrahepatic procedures: 15	≤ or > 8 weeks		17.9 vs 26.3 (p=NS)	2.6 vs 5.3 (p=NS)	- -	- -	5.3 vs 2.6 (p=NS)	10.3 vs 7.0 (p=NS)	- -	- -	3.5 vs 2.6 (p=NS)
[26]	Gruenberger JCO 2008	56/56	Liver resection only 41 → Major hepatectomies (≥3segm): 36% Synchronous primary tumor + liver resection 11	5w.	-	2.0	2.0	- -	2.0	0.0	4.0	2.0	6.0 Sepsis	0.0
[40]	D'Angelica Ann Surg Oncol 2007	32/64	Hepatectomy 32 →Major hepatectomy (≥3segm) 17 →in addition to hepatectomy: RFA 1 Cryoablation 2 Biliary resection + HJS 1 Synchronous hepatic + colorectal resection: 9	Median 6.9 weeks range [3-15]	Median 7.4 weeks range [5-15]	0.0	-	-	-	0.0	0.0	0.0	6.25 abscess	0.0
B. Other major surgery														
[28]	Kozloff *BRiTE* The Oncologist 2009	521/1953	Major surgery: -abdominal 157 -hepatectomy 88 Minor surgery: 67	"within 90 days"	-	-	-	-	-	-	4.4	1.5	-	-
[33]	Scappaticci J Surg Oncol 2005	305/1132	Bowel surgery 28 Exploratory laparotomy 8 Non-GI surgery 17 Abscess/fistula drainage 7 Hepatic metastasectomy 4 Other GI 7 Unknown 4	Major / emergency surgery during BV	-	- -	2.7 vs 0.0	2.7 vs 0.0	1.3 vs 3.4	2.6 vs 0.0	1.3 vs 0.0	1.3 vs 0.0	- -	2.7 vs 3.4
[36]	Willett JCO 2005	5	LAR 4 APR 1	7-9 weeks	-	-	20.0	0.0	0.0	0.0	0.0	0.0	20.0	-
[6]	Willett Nat Med 2004	6	Resection rectal cancer 6	7 weeks	-	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
C. Minor surgery														
[37]	Zawacki J Vasc Interv Radiol 2009	189/1082	Venous access port 195	7-44 days	1-44 days	-	-	-	-	-	3.2	4.2	-	-

Tables 3, 4 & 5:
p-values: mentioned if available
ng: not given; p=NS: statistically not significant; TTS: time to surgery, i.e. the time interval between discontinuation of BV and surgery; TpS: time post surgery, i.e. the time interval between surgery en (re)start of BV; N surgery +BV / total= number of patients undergoing surgery during or after BV-based treatment over the total population