and metastatic liver cancer. We examined the records of these patients to determine (1) the incidence, management, prophylaxis of complications associated with surgical placement of these devices and (2) the overall usability time of devices.

Results: There was no operative mortality in this series. Operative or early (within 30 days) complications occurred in 5 patients (5.2%). Late complications occurred in 27 patients (28.4%). Irreversible loss of device function were observed only in 4 patients (4.2%) and was mainly related to hepatic artery thrombosis. In most cases loss of function was reversible by medical or surgical management. The hepatic artery perfusion could be performed in 90, 83 and 76% of the patients to be infused at 6, 9 and 11 months.

Conclusions: Placement of hepatic arterial device represents a safe method to deliver regional chemotherapy. No life threatening complications and a low rate of early postoperative complications were observed. Although late complications occurred in 28% of the patients, only in four cases they were accompanied by irreversible loss of device function with impossibility to deliver regional chemotherapy. These patients were candidates for systemic chemotherapy

735 POSTER

Bcl-2 expression is reduced and reciprocal to *p53* and *c-myc* expression in advanced human colorectal cancer

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Purpose: Apoptosis inhibition may be a strategy by which mutated cells evade normal clearance mechanisms and lead to development of colorectal cancer (CRC). We determined the expression of the apoptosis inhibitor bcl-2 in normal colon mucosa and 21 CRC metastases by RT-PCR analysis and correlated it to p53 and c-myc expression in the same samples.

Methods: Material from 21 liver CRC metastases was obtained at surgery, and total RNA was extracted and reverse transcribed into c-DNA. The target genes bcl-2, p53 and c-myc were amplified together with b-actin and b-2Microglobulin using published primers in differential PCR reactions, and the ratios between target genes in metastases and normal colon mucosa were determined.

Results: Compared to normal mucosa controls (= 1U), the relative bcl-2 mRNA expression was lower in CRC metastases (mean 0.45 U, $p < 0.0001$. p53 expression was reciprocal to bcl-2 expression ($p = 0.021$) in 19 evaluable samples. In tumours overexpressing p53 (more than two-fold elevated over normal controls), bcl-2 mRNA was significantly decreased ($p = 0.0052$). c-myc was also inversely correlated with bcl-2 expression ($p = 0.025$).

Conclusion: bcl-2 mRNA expression is reduced in CRC metastases compared to normal mucosa. bcl-2 is reciprocally expressed to p53 and c-myc, two genes also involved in apoptosis and altered late during colorectal tumorigenesis. This inverse correlation suggests an active down-regulation of bcl-2 following possible delegation of its apoptosis inhibiting function to other genes.

736 POSTER

Consistent safety and efficacy results in 2 study populations treated with Irinotecan (CPT-11) for metastatic colorectal cancer (MCRC) resistant to 5-FU

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The DNA Topoisomerase I inhibitor irinotecan (CPT-11) has shown outstanding activity in MCRC refractory to 5-Fu. We have compared the safety and efficacy profile of CPT-11 in 2 studies: a confirmatory European study (A, CPTV222) and a pragmatic French post approval study (B, CPTF225). Duration of infusion ranged from 30 to 120 minutes. 109 patients (pts) were included in A and 138 in B. Respectively, 588 and 614 cycles were administered. Demographic data were comparable in both studies, and all pts had progressive disease at study entry.

Drug Exposure: The median no. of cycles was 6 (1–12) in A and 5 (5–6+) in B, the relative dose intensity was 0.97 (0.61–1.08) and 0.96 (0.49–1.09), respectively.

Safety: Dose limiting toxicities of CPT-11 are concomitant febrile neutropenia (FN) and delayed diarrhoea (DD) which were observed in 2.7% of pts in A and 4.3% in B, perhaps due to poorer prognostic factors at study entry in B.

Efficacy: RR was 14% in A and 12% in B, tumour growth control (OR + SD) was demonstrated in 58% of pts in A and 65% in B. No difference in parmacokinetic analysis was observed between duration of infusion (30 vs 120 minutes) regarding clearance, Vdss of CPT-11 and AUC's of SN38/SN38G.

737 POSTER

De-*O*-acetylation of adhesion molecule sialyl-LE^x correlates with colorectal carcinoma progression

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Purpose: Sialy-Le^x (sLe^x) belongs to carbohydrate antigens whose expression gradually increases in the course of human colorectal carcinoma progression. We investigated the effect of *O*-acetylation on sLe^x accessibility in mucins isolated from normal colonic tissue, colon carcinomas and their liver metastases.

Methods: SLe^x positive mucins were purified from the fresh frozen tissue (each n = 10) on three CsCl gradients and separated by SDS page. SLe^x was detected on Western blots with AM3 antibody prior and after de-*O*-acetylation with 0.1 NaOH and quantified by densitometry. Additionally the percentage of *O*-ace-tylated sialic acids was analysed in HPLC.

Results:

	Normal	p	Tumor	p	Metastas.
Western signal prior NaOH	1.6 a.u	**	48 a.u.	*	83 a.u.
Western signal after NaOH	100 a u		110 a.u.		115 a.u.
Signal increase after NaOH	98 a.u.	**	62 a u.	**	32 a u.
O-acetyl. sialic acids	62%	*	43%	*	22%

Mann-Whitney U-test: * = $p < 0.05$, ** = $p < 0.01$

Conclusion: This data indicate, that the overexpression of mucin-bound sLe^x is due to the gradual decrease of sLe^x *O*-acetylation. This chemical modification represents a novel marker of colon carcinoma progression. Since high expression of sLe^x has been associated with tumor cell capacity to metastasize, the present data pose the question how far the sialic acid de-*O*-acetylation is facilitating the metastatic process *in vivo*.

738 POSTER

Addition of oxaliplatin (Eloxatine®, LOHP) to the same leucovorin (LV) and 5 fluorouracil (5FU) bimonthly regimens after progression in patients (pts) with metastatic colorectal cancer (MCRC): Preliminary report

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Foltox 2, a bimonthly regimen of high-dose (HD) LV, with HD 48 hour (h) continuous infusion of 5FU and LOHP at 100 m/sqm, produced a 46% response rate (RR) in 5FU pretreated pts with MCRC (Eur J Cancer, in Press). A multicentric Ph II study was started in 10/95 with a lower dose of LOHP to decrease the toxicity. *Eligibility/Protocol:* MCRC pts with third party reviewed proof of progression on HDLV/5FU, LOHP: 85 mg/sqm 2 h iv dl is added to LV: 200 mg/sqm 2 h iv d1,2+ 5FU: 400 mg/sqm iv push d1,2; 5FU: 600 mg/sqm 22 h civ d1–2 = (*Folfox3*); or to LV:500 mg/sqm 2 h iv dl, 2+5FU: 1.5 g/sqm 22 h civ d1–2 = (*Folfox4*) to be repeated q2 weeks until PD or limiting toxicity. Pts: 100 pts were accrued/49 assessable, 17 F/32 M, median age: 62 y [32–74], median PS (ECOG): 0 [0–2], sites involved: 1 = 24, 2 = 16, ≥3 = 9. *Toxicity* (%cy/%pt): 364 cy/46 pts were evaluable. Median cy/pt: 6 (1–16+), median dose of LOHP: 510 mg/sqm (255–1360+). Neurological (specific scale): Gr2: 13/26, Gr3: 1.5/6.5. Other (CTC): WBC Gr3: 1.5/11, Hb Gr3: 0.5/2, Plt Gr3. 1.5/11, Vomiting Gr3: 1/6.5, Diarrhea Gr3: 0.5/2, Mucositis Gr3. 2/13, *Activity* (WHO): Objective RR by third party review: 44 eligible evaluable/49 pts [non évaluable: 5 (not resistant. 2, refusal: 2, second cancer: 1], were: