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:

	Folfox 3: 24 pts	Folfox 4 20 pts	All: 44 pts
Pts (PR/SD/PD)	5/9/10	7/4/9	12/13/19
RR% [CI]	21 [7 1–42.1]	35 [15 3–59.2]	27 [14.9–42.7]

These preliminary results confirm previous reports of L-OHP preclinical and clinical synergy with 5FU in 5FU resistant MCRC. A new study with L-OHP at 100 mg/sqm is planned to elucidate eventual LOHP dose-response relationship.

739 POSTER

The value of postoperative surveillance after radical surgery for colorectal cancer

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Purpose: Early detection of recurrence after curative resection for primary colorectal cancer (CRC) should improve patients' (pts) prognosis. The present cohort study was aimed at assessing the effectiveness of systematic follow-up in pts with CRC, both regarding the rate of tumour recurrence amenable to curative-intent surgery and survival.

Methods: Between July'87 and June'90, 199 CRC pts who underwent radical surgery were followed according a previously well-defined post-operative surveillance programme which consisted on laboratory studies (including serum CEA assay) every 3 months, physical examination and abdominal ultrasound or computed tomography every 6 months, and chest radiograph and total colonoscopy once a year. Cohorts were defined according patients' compliance to the follow-up protocol.

Results: One hundred forty pts (70%) were considered to be compliant with the surveillance programme (cohort A), while the remaining 59 pts occasionally attended follow-up investigations (cohort B), both cohorts being similar with regards baseline characteristics. Although there were no differences in the overall recurrence rate (38% vs 41%; ns), curative-intent reoperation was possible in 18 pts (34%) of those with tumour recurrence in the cohort A, but in only 3 pts (12%) in the cohort B ($p = 0.05$). Similarly, the probability of survival was higher in the cohort A, both regarding overall (63% vs 37% at 5 years; $p < 0.001$) and CRC-related (69% vs 49% at 5 years; $p < 0.02$) rates. Cox regression analysis disclosed that only a more advanced Dukes' stage (OR: 8.17, 95%CI: 1.13–59.29) and non compliance with the postoperative surveillance programme (OR: 2.32, 95%CI: 1.50–3.60) had an independent negative impact on survival.

Conclusions: Systematic postoperative surveillance in pts with CRC operated on for cure increases both the rate of tumour recurrence amenable to curative-intent surgery and survival.

740 POSTER

Significance of matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 3 (MMP-3) expression during liver metastasis in colorectal cancer

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Purpose: Degradation of extracellular matrix is considered to be essential process for tumor invasion and metastasis. Activities of matrix metalloproteinases (MMPs) which has a capability of degradation of all matrix components are regulated by activators and inhibitors such as tissue inhibitors of metalloproteinases (TIMPs). Our previous study showed that pro MMP-9 was activated by MMP-3 directly. To clarify clinical significance of MMP-9 and MMP-3 expression in colorectal cancer, we have studied MMP-9 and MMP-3 expression immunohistochemically.

Methods: Paraffin embedded spicemens from 194 patients with colorectal cancer who were underwent operation between 1988 and 1991 were immunostained for MMP-9 and MMP-3.

Results: MMP-3 was localized only in stromal cells such as monocyte, macrophages, whereas MMP-9 was noted in both tumor cells and stroma. The incidence of MMP-9 expression in the tumor cells was 39.7% and that of MMP-3 in the stroma was 22.2%. There were strong relationship between liver metastersis and the expression of MMP-9 and/or MMP-3. In interest colon, both enzymes significantly coexpressed.

Conclusion: MMP-9 and MMP-3 may play an important role in liver metastasis and tumor invasion. In particular, MMP-3 may act as an activator for proMMP-9.

741 POSTER

The identification of high risk patients with metastatic colorectal cancer

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Purpose: Identification of prognostic factors in metastatic colorectal cancer.

Methods: Four hundred and seventy seven previously untreated patients (pts) who were randomized in two consecutive phase III trials of the EORTC Gastrointestinal Tract Cancer Cooperative Group (high-dose 5-FU (HD-5FU) ± low-dose methotrexate (LD-MTX) and HD-5FU/LD-MTX ± LD-PALA) were included in the analysis. The Cox model was used for the analysis.

Results: The median duration of survival for all patients was 12 months. Prolonged survival was observed for patients who had a longer duration since first diagnosis ($p = 0.001$), rectum as the primary tumor site ($p = 0.035$), good performance status ($p < 0.001$), none or little weight loss ($p < 0.001$), initial white blood cells $\leq 8 \times 10^9/l$ ($p < 0.001$), initial granulocyte count $\leq 5 \times 10^9/l$ ($p < 0.001$), initial platelet count $\leq 350 \times 10^9/l$ ($p < 0.001$), normal hemoglobin level ($p = 0.001$), normal serum bilirubin ($p = 0.021$) and normal alkaline phosphatase ($p < 0.001$). The multivariate model retained the following factors of poor prognosis: thrombocytosis ($p < 0.001$), weight loss ($p < 0.001$), abnormal serum bilirubin level ($p < 0.001$) and granulocytosis ($p < 0.001$). There was evidence that the effect of the initial granulocyte count on survival was more prominent during the first year.

Conclusion: Some biological variables are important prognostic factors for survival in patients with metastatic colorectal cancer. These factors should be taken into consideration in the design of new trials.

742 POSTER

Sphincter-saving operations for cancer localised in the distal half of the rectum

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Purpose: The goal of this prospective study is to present the broad use of the sphincter saving operations for treatment of rectal cancer, localised in the distal half of the rectum.

Materials and Methods: In order to determine the usefulness of sphincter – saving operations were analysed 784 patients operated radically on rectum cancer at the Dept. of Surgery in NCO for the period from 1.1.1984 to 31.12.1996. Discussed are the techniques, clinical observations and post-operative results in the seven most widely used in our clinic sphincter-saving operations.

Results: The authors emphasised upon the very low percent of the local recurrences for 5 years follow up 5.3 ± 1.1%. This is one of the lowest percent of local recurrences after sphincter-saving operations of the rectum for cancer in the literature. Discussed are the indications for bilateral lymphatic dissection and for excluding the bowel passage with transversostomy. The anal continence was satisfactory in all of the applied methods (proved tonometrically).

Conclusion: The methods introduced in our clinic for cancer treatment in the distal rectum half not only increased the number of the sphincter-saving operations, but decreased considerably the postoperative complications. All this give us a guarantee not only to continue to apply them, but to propose them for broader application in the everyday practice.

743 POSTER

Treatment of liver metastases and moderate peritoneal carcinomatosis by hepatectomy and cytoreductive surgery followed by immediate postoperative chemotherapy: Feasibility and preliminary results

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The purpose of this study is to report tolerance, and preliminary results in patients with liver metastases synchronous to moderate peritoneal carcinomatosis, treated with a hepatectomy and complete cytoreductive surgery, immediately followed by postoperative intraperitoneal chemotherapy. Twleve patients with liver metastases, and moderate pertioneal carcinomatosis were included in the study. They all had liver resection for metastases, complete cytoreductive surgery of the peritoneal carcinomatosis, and immediate