with B Dukes cases since it contributes to identify a subset of patients that may benefit from adjuvant therapy.

730 POSTER

## Anal carcinoma: Regional recurrences dependent on target volume of sphincter-sparing radio-/chemotherapy

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**Purpose:** Different volumes are published for radical RT of anal ca. Including only the small pelvis into the ref vol., we examined whether this PTV is sufficient enough for the prevention of pelvic recurrences (REC).

**Patients:** From 1979-Oct 1996, 80 pts (56 f, 24 m, median age 66 yrs) with anal ca were treated for sphincter sparing with RT (80 pts) and ChT (52/80): T1 19 pts, T2 34 pts, T3 21 pts, T4 5 pts, N1-3 14 pts; 55 with biopsy, 21 with excision and 4 with LN-excision. RT was mostly given with two parallel opposed fields, SD 1.8 Gy, TD 45 Gy, with concomitant ChT in week 1 (5-FU 1000 mg/m$^2$, d 1–5; Mito-mycin-C 10 mg/m$^2$, d 1) and 5 (5-FU 1000 mg/,m$^2$, d 29–34). For 48 pts, interstitial LDR-brachytherapy (BT) was used as a boost, but replaced 1995 by endocavitary HDR-BT (14 pts). 15 pts had an e$^-$ boost. The time gap of 6 wks between RT and boost was changed to two wks after 1990.

**Results:** 17 out of 80 pts developed a loco-regional REC. 11/17 pts had a local REC, 5/53 T1/2 tumours (9.4%) and 6/26 T3/4 tumours (23%). Shortening the treatment time reduced the REC-rate, p = 0.06. 11/17 pts had a regional REC (5x with local REC). Two inguinal and one presacral REC were not covered by the PTV. All pelvic RECs developed inside the PTV, i.e. inside the small pelvis, below the iliacal bifurcation.

**Conclusions:** The PTV, covering only the small pelvis, has proved to be sufficient in preventing pelvic regional recurrences. There was no pelvic recurrence outside this volume.

731 POSTER

## Immuno-chemoembolisation in the treatment of colorectal livermetastasis

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**Introduction:** Intra-arterial chemotherapy of colorectal livermetastasis leads to an elevation in cytostatic drug concentrations and higher remission rates. The aim of this study was to evaluate the efficiency of a combination of intra-arterial immunotherapy and chemotherapy. In order to activate the hepatic immunsystem we used Granulocyt-Macrophages Stimulating Factor (GM-CSF) intra-arterially.

**Methods:** Up to now we treated 34 patients (28 male/6 female) with isolated colorectal livermetastasis by two cycles of intra-arterial immuno-chemoembolisation. 12 out of 34 patients were previously treated by systemic chemotherapy and two patients by regional chemotherapy. Treatment consisted of 150 mcg GM-CSF applicated at day one and two, 1000 mg 5FU applicated on day three and four and 40 mg melphalan as embolisation in combination with lipiodol and gel-foam via an angiographicly placed hepatic-artery system. Treatment free interval was 28 days, re-evaluation for remission was done four weeks after the second cycle according to WHO-criteria.

**Results:** In 34 patients we saw 5 complete remissions, 5 CR after downstaging and resection and 20 PR In two cases there was a stable disease leading to an overall remission rate of 89%. Sideeffects were usually low and acceptable mostly correlated to chemoembolisation with vomiting 13.5%, abdominal pain 17.3% and transient elevation of the liver enzymes 13.5%. Interestingly there was a very low rate of leucopenia not exceeding WHO-grade II of 3.9%. One year survival rate is 92%.

**Conclusion:** The intra-arterial application of GM-CSF in combination with cytostatic chemotherapy is possible without any strong local or systemic side effects. This method leads to a high local remission rate. Further studies have to evaluate the efficiency of intra-arterially applicated GM-CSF for the hepatic immunsystem leading to a higher level of cytocines in the hepatic tissue.

732 POSTER

## Peritoneal carcinomatosis treatment with curative: Institut Gustave-Roussy experience

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**Purpose:** The aim of this study is to report the results of a phase II study in which the PC was treated with complete cytoreductive surgery associated with the treatment of the residual microscopic disease by immediate intraperitoneal postoperative chemotherapy (IIPC) for five days (Mitomycin®, Fluorouracil®, Adriamycin®, and Platinol®).

**Methods:** Fifty-four patients with a PC from miscellaneous origins were treated between January 1993, and April 1996. The PC was important (clinically evident), but extraperitoneal localization free, in 29 cases. The PC was fortuitously discovered during a laparotomy for extraperitoneal cancer localization in 25 cases. Operative time was 7:21 hours, associated with extensive peritonectomies, and resection of invaded organs (4 organs per patient). IIPC was complete (5 days) in 91% of patients.

**Results:** Three postoperative deaths (5.5%) were reported. Morbidity was present in 61% of patients, and was related to surgical extension ($p < 0.001$). Two-years survival of 50% was correlated with the importance of the PC ($p < 0.01$), and was the same for both groups of patients (isolated PC *vs.* moderate PC associated with extraperitoneal localization). PC recurrence rates were 30% at two years.

**Conclusion:** Complete cytoreductive surgery associated with IIPC is a logical and promising treatment of PC. However, it appears that: it is a heavy treatment for patients (and physicians), and its lawfulness will be proved only after a randomized study (currently going).

733 POSTER

## Intraoperative radiotherapy (IORT) for recurrent rectal carcinoma

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**Purpose:** Curative treatment for recurrent rectal carcinomas is possible in less then 10%. A multi-modality treatment using IORT was evaluated.

**Materials and Methods:** A total of 31 patients suffering from a recurrent carcinoma in the pelvis had IORT (minimum follow-up 18 months). Multivisceral or anterior resection (n = 8) yielded a R0-resection in 16 pat. In equally 8 pat. microscopically or macroscopically residual tumor remained. The mean IORT-field size was 7.4 (5–13.2) cm, the mean IORT-dose 13.7 (10–20) Gy. External beam radiotherapy (EBRT) was given with 41.4 Gy (1.8 Gy SD) either preoperatively (n = 21) or postoperatively (n = 10). 22 pat. had simultaneously chemotherapy.

**Results:** After a median follow-up of 28.2 months 8 pat. died due to progressive disease. 1 pat. died without tumor. 8 pat. suffered from a second local failure, while 3 of these patients developed additionally distant metastases. 7 pat. had distant metastases alone. After non-complete resection the failure rate was significantly higher, due to a higher distant metastases rate (20% vs. 62%). The actuarial 5-year-overall survival was 55% for the entire patient group.

**Conclusion:** Compared to historical controls local tumor control and overall prognosis was improved. Locally restricted dose application with IORT offers optimum normal tissue sparing to further improve the benefit of multi-modality treatment strategies.

734 POSTER

## A seven-years experience with implantable devices for regional hepatic arterial chemotherapy: Usability time, incidence and management of complications

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**Background:** The successful delivery of chemotherapeutic drugs through an implantable hepatic arterial device depends on the surgeon's understanding of hepatic arterial anatomy, proper cannulation technique and operative as well as postoperative measures to decrease the occurrence of complications. We reviewed the usability of hepatic arterial ports at our department.

**Methods:** Between March 1st, 1989 and December 31th, 1996 we placed 123 implantable hepatic arterial devices in 95 patients with primary

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: