a period of 24-h, and dichotomy index (I < O), quantifying the differences in activity distribution between the rest span and the active phase. Paired rhythm parameters at C0 and C4 were compared by Wilcoxon signed rank test.
Results: Median values and quartile distribution [1st-3rd] of the 3 circadian rest/activity rhythm parameters were not significantly different at baseline (C0) and after 4 courses of CHT (C4) (Table 1). After CHT, however, the number of pts remaining in the same tercile ranged from 44 to 53%, according to the parameter (34 pts for r24, 40 for I < O, and 41 for mAct). Among the remaining pts, after 4 courses of CHT, the rhythm parameters significantly improved or deteriorated in nearly half of the pts each (20 and 23 for r24, 19 and 18 for I < O, 17 and 19 for mAct, respectively).
Conclusions: The main chemotherapy regimen for colorectal cancer modified the rest/activity circadian rhythm in nearly half of the patients in opposite directions. This supports large interpatient variability in response of the circadian timing system to chemotherapy. Understanding the relations between circadian system status and treatment-related toxicity and efficacy will lead to improve the therapeutic index through tailoring delivery schedule to the individual features of the patient.

Table 1

	Range of variation	C0	C4	p
r24	−1.0 to 1.0	0.41 [0.25–0.55]	0.45 [0.25–0.57]	0.34
I < O	0 to 100	97.5 [92.2–99.2]	98.2 [95.6–99.3]	0.15
mAct	0 to ∞	112 [90–127]	112 [86–132]	0.88

Publication
GI – colorectal cancer

663 PUBLICATION

Prognostic index for adjuvant treatment in locally advanced rectal cancer after preoperative chemoradiotherapy and radiotherapy

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Background: Preoperative radiotherapy and chemoradiotherapy lower the risk of local recurrence and improve survival in stage II and III rectal cancer. After preoperative treatment is this initially homogeneous group stratified and patients have different relapse rate and survival.
Methods: A total of 174 patients (34% women and 66% men) with locally advanced rectal adenocarcinoma were treated with preoperative radiotherapy or chemoradiotherapy and retrospectively evaluated. The median follow up is 24 months (range 3–74 months). All patients received preoperative external beam radiation (40–50 Gy/20–25 fractions/4–5 weeks) using linear accelerator and 3D planning. Concomitant CHRT with 5-FU was carried out in 25% of patients. The data were analysed with statistical software SPSS version 10.0.
Results: Radical resection underwent 86% of patients, non-radical tumor resection 2% and inoperable tumor persisted in 7% (at the beginning it was 13% of patients). Distant metastases were detected peroperatively in 5%. Statistically significant factors that influence both overall and disease free survival are postradiotherapy stage ($p = 0.005$), postradiotherapy grading ($p < 0.001$), angioinvasion or perineural spread ($p = 0.023$), radicality of surgery ($p < 0.001$) and gender ($p = 0.036$). Local recurrence was associated in preradiotherapy T4 tumors ($p = 0.048$) and angioinvasion or perineural spread (0.049). Two-year OS was 85% and 5-year OS was 60%. Prognostic index is calculated from prognostic factors (stage, radicality of surgical procedure, grade, angionvasion and distance from the anal verge) and overall score devides patients into 4 groups with different relapse risk and OS. Excellent prognosis is achieved in patients of low risk group (radical surgery, pT1-pT2 good differentiated tumors with negative lymphnodes, no angioinvasion, no perineural spread, or complete remision after preoperative treatment), this group counts for 14% of all patients and 2-year DFS and OS and 5-year DFS and OS are 100% (all patients are alive without recurrence). Patients with intermediate risk have a 5-year OS 80%, patients with high risk of relapse have 5-year OS 55% and in group of very high risk no patient survived 5 years.
Conclusion: Patient with low risk relapse have relapse risk less than 5% and in our institution adjuvant chemotherapy in this low risk group after preoperative radiotherapy is omitted.

664 PUBLICATION

Cetuximab in combination with irinotecan/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFIRI) in the first-line treatment of metastatic colorectal cancer (mCRC)

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Background: FOLFIRI is a standard option in the first-line treatment of mCRC. Cetuximab (Erbitux®) is an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR), which is commonly expressed in mCRC. Cetuximab is active in mCRC patients failing on irinotecan-based therapy. This phase I/II trial investigated the safety and efficacy of cetuximab+FOLFIRI in the first-line treatment of EGFR-expressing mCRC.
Materials and Methods: Patients with immunohistochemistry-determined EGFR-expressing mCRC, who had not been treated for metastatic disease, received cetuximab (initial dose 400 mg/m^2 followed by 250 mg/m^2/week). FOLFIRI was given every 2 weeks: irinotecan 180 mg/m^2, FA 400 mg/m^2 and 5-FU 300 mg/m^{2}bolus plus 2,000 mg/m^2/46-h infusion (low-dose, LD) or 400 mg/m^{2}bolus plus 2,400 mg/m^2/46-h infusion (high-dose, HD). The use of LD 5-FU was part of the early dose-finding phase of the study.
Results: This analysis was performed on the per-protocol HD population of 42 patients: 64.3%/35.7% male/female, mean age 60.0 years, median KPS 100, 79% colon primary tumour. There were 19 confirmed objective responses (all partial responses [PR]) (45.2%) and 16 patients with stable disease (SD) (38.1%), giving a disease control rate (complete response+PR+SD) of 83.3%. The median response duration was 306 days (10 months), and median survival was 699 days (23 months). 10 patients (23.8%) were able to undergo resection of metastases for curative intent, 9 of whom had liver metastases. There were 8 R0 resections. Treatment was well tolerated. 66.7% of the 42 patients experienced grade 3/4 adverse events, the most frequent of which were leucopenia (16.7%), diarrhoea (14.3%), vomiting and intestinal obstruction (11.9% each), skin rash and abdominal pain (9.5% each), and asthenia and dyspnoea (7.1% each).
Conclusions: Cetuximab+FOLFIRI, incorporating high-dose 5-FU, is a feasible and active combination for the first-line treatment of EGFR-expressing mCRC. 45.2% of patients achieved an objective response. The median survival was 23 months and 23.8% patients were able to undergo resection of initially unresectable metastases. Based on these results, a new phase III trial was started.

665 PUBLICATION

Phase I/II study of 24-hour infusion of irinotecan (CPT-11) in combination with sequential oral leucovorin (LV) and uracil/tegafur (UFT) for patients with metastatic colorectal cancer

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Background and Objective: A combined therapy using irinotecan (CPT-11), 5-fluorouracil (5-FU) and leucovorin (LV) is one of the standard chemotherapies (CT) for metastatic colorectal cancer (MCRC). The cytocidal effect of CPT-11 is specific to the S phase of the cell cycle. Therefore, its antineoplastic effect may be greater when administered in small dosages over an extended period, rather than when given at larger dosages for a shorter period. It has been reported that when a combination of 5-FU and CPT-11 is given sequentially it is more effective than when given concurrently. The effects of an oral administration of a combination of uracil/tegafur (UFT) and LV and an intravenous infusion of 5-FU combined with LV are comparable but the former is more convenient. Therefore, for a Phase I/II study, a schedule in which 24-hour continuous infusion of CPT-11 followed by sequential oral administration of UFT/LV was selected.
Methods: The subjects were patients (pts) who had MCRC with measurable lesions. Prior CT or adjuvant CT was allowed when they were interrupted at least 4 weeks before beginning this study. Each course was composed of the following: 24-hour infusion of CPT-11 on days 1 and 15: and oral UFT and LV divided into 3 parts were given on days 3–7, 10–14, 17–21 and 24–28. This regimen was repeated every 4 weeks. The dosages given during the Phase I study are shown in the table below. The maximum tolerated dose (MTD) was based on the dose-limiting toxicity (DLT) of the first course: the dosages one level below the MTD was adopted for the recommended dosage (RD) in the Phase II study.
Results: Three pts each were assigned to levels 1 and 2. No DLT was recognized in any of them. At level 3, 3 of the 6 pts developed a DLT, i.e.,

grade 3 diarrhea; so this level was determined as MTD. Level 2 was set as RD. A Phase II study is now ongoing and 16 pts were assigned to level 2 up to now. Altogether, 22 patients (including 5 pts with prior CT and 12 pts with adjuvant CT) had received a total of 101 courses and were available for the evaluation of the results. CR was noted in 2 pts and PR in 12 pts, for a response rate of 64% (14/22). Grade 3 leucopenia occurred in 2 pts, G3 anemia in 1 pt, G3 diarrhea in 6 pts, G3 nausea in 5 pts, G3 vomiting in 4 pts. None suffered G4 toxicity.
Conclusion: It was suggested that a combination therapy of 24-hour continuous infusion of CPT-11 and sequential oral UFT/LV appeared to be well tolerated and shows high efficacy for MCRC.

	CPT-11 (mg/m^2/day)	UFT (mg/m^2/day)	LV (mg/body/day)
Level 1	100	233	75
Level 2	100	300	75
Level 3	110	300	75
Level 4	120	300	75

666 PUBLICATION

Anatomical segmentectomy (SGX) is the oncologic equivalent of hemi-hepatectomy (H-HPX) for the treatment of small volume unilobar colorectal liver metastases (CLM)

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Introduction: HPX is the only potentially curative treatment for CLM. As methods of detection of CLM and awareness of the benefits of HPX improve, smaller volume disease is being diagnosed increasingly. Historically, most patients underwent H-HPX, but the recent trend is towards more local resections towards increasing hepatic preservation. Furthermore, many patients with initially inoperable disease are now coming to HPX (often SGX) after successful downstaging with systemic chemotherapy. This trend raises questions of oncological benefit, whether this approach increases the risk of residual disease in the ipsilateral remnant liver. This study examines the site of liver only recurrence (LOR) with particular reference to ipsilateral-LOR after unilateral SGX.
Methods: Prospectively collected single centre 5-yr follow-up of 184 patients post-HPX for CLM. Data stratified for type of surgery, survival, LOR (ipsilateral, contralateral, bilateral).

Results

	No. pts	% Op. Mort.	Ipsilat LOR	Contra/Bilat LOR	5 year survival %
Unilat SGX	98	0	13	13	44
Bilat SGX	29	0	–	23	21
Hemi-HPX	27	3	–	15	34
Extended-H-HPX	31	3	–	19	26

5 patients underwent re-HPX for recurrent LOR after unilateral SGX. There were no re-HPX for LOR in any of the other groups.
Conclusions: 13/98 (13%) of LOR were ipsilateral, 29/98 (28%) were contra or bilateral after unilateral-SGX. Since 57/85 (67%) LOR were either contralateral or bilateral following either bilat-SGX or H-HPX, then these data would support the continuing use of unilateral SGX for small volume unilateral CLM.

667 PUBLICATION

Capecitabine and oxaliplatin (XELOX) in combination with bevacizumab in the treatment of metastatic colorectal cancer: results of a phase II trial

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Background: Bevacizumab (BV) improves survival when added to first-line (5-FU/LV and IFL) and second-line (FOLFOX) chemotherapy for metastatic colorectal cancer (mCRC). The FOLFOX regimen is superior to bolus IFL, but requires the use of an ambulatory infusion pump. Capecitabine, an oral fluoropyrimidine, is a convenient alternative to 5-FU. We designed a phase II trial to investigate the safety and efficacy of capecitabine and oxaliplatin in combination with BV (XeloxA).
Methods: Patients (pts) with untreated mCRC received oxaliplatin 85 mg/m^2 day 1, capecitabine 1000 mg/m^2 bid days 1–5 and 8–12, and BV 10 mg/kg day 1 of a 2-week cycle. The starting capecitabine dose was changed to 850 mg/m^2 bid due to toxicity in the first 27 pts. The primary endpoint was response rate. Safety was analysed for excess 60-day mortality (>15%) or grade 4 adverse events (>50%). Data were analysed using the intent to treat method.
Results: 30 pts have received therapy: 16 men, 14 women; median age 55.2 (range 24–76); all performance status 0. Grade 3 diarrhoea was seen in 30% of pts; no pt experienced grade 4 diarrhoea. Of 3 pts started at the 850 mg/m^2 bid capecitabine dose, none have experienced >grade 1 diarrhoea. Hand–foot syndrome (HFS) was seen in most pts; 6/30 (20%) with grade 1, 12/30 (40%) with grade 2 and 1/30 (3%) with grade 3 HFS. Other toxicities were minimal, including grade 3 neutropenia (7%), grade 3 nausea and vomiting (7%), and grade 3 peripheral neuropathy (10%). 20 pts (66%) required at least one capecitabine dose reduction, and 12/30 (40%) required 2 or more reductions during treatment, typically for diarrhoea and/or HFS. There were 16 partial responses and one complete response (RR 57%; 95% CI: 37–75%); 11 (37%) pts had stable disease. Median TTP was 11.9 months (95% CI: 9.8-∞).
Conclusions: The initial capecitabine dose used in this trial was decreased due to toxicity, primarily HFS and diarrhoea, and appears to be better tolerated. Preliminary evidence suggests that the XeloxA regimen is highly active. This is supported by response data from a randomised phase II trial [Hochster et al. J Clin Oncol 2005;23 (June 1 Suppl): Abstract 3515]. The reported median TTP is among the highest obtained in the first-line treatment of metastatic colorectal cancer. Insights into management of pts on long-term therapy will be reported. Enrollment continues to a planned accrual of 50 pts.

668 PUBLICATION

Concurrent irinotecan, oxaliplatin and uft/lv triple therapy as first-line treatment for advanced colorectal cancer (ACRC)

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An open label dose-finding study of concurrent irinotecan (Ir), oxaliplatin (Ox) and oral UFT/LV was conducted in patients (pts) with ACRC. The aim was to find a recommended dose while providing an efficacious treatment in a first-line setting, which was well tolerated by alternating the Ir with the Ox every 2 weeks. All pts received Ir (d1), Ox (d15) and UFT/LV on days 1 to 21 of a 28-day cycle. Using conventional dose escalation criteria, pts were treated in cohorts of 3 and in the absence of grade 3 toxicity (assessed at 1 month), pts were entered at the next dose level (DL). There was no intra-pt dose escalation.

	UFT (mg/m^2/day)	Ir (mg/m^2)	Ox (mg/m^2)
DL-1 (6 pts)	200	180	85
DL-2 (6 pts)	250	180	85
DL-3 (9 pts)	250	180	100
DL-4 (4 pts)	300	180	100

The intended duration of chemotherapy was 24 wks, with response evaluation every 8 wks. 25 pts, median age 63 (range 24 to 79) with WHO PS 0 to 2, were recruited between Feb 2004 to Apr 2005. All pts had measurable disease with a median of 4 marker lesions at baseline (range 1 to 10). At DL-4, 4/4 pts suffered multiple grade 2 toxicities and 3/4 a grade 3 toxicity. Diarrhoea, lethargy and vomiting were the dose-limiting toxicities (DLT). 3 pts were initially entered at DL-3 and a further 6 pts were then entered once the MTD had been reached. At this dose-level, 3/9 pts endured grade 2 toxicities and 1/9 a grade 3 toxicity. One pt (PS 2) who had extensive disease was admitted 5 days after the first dose of chemotherapy (DL-1), with neutropaenic sepsis which was thought to be highly atypical; a question of DPD deficiency was raised. A further pt, also at DL-1, who had demonstrated a PR by RECIST criteria, died from a cardiac event in the third month of treatment. He had no prior cardiac history and no symptoms of angina during the chemotherapy. At this time, 19 pts are evaluable for response giving an ORR of 68% and tumour control rate of 79% (PR- 13, SD- 2, PD- 4). The median duration of response has not been reached. One pt with residual lymph node disease, is awaiting XRT and another patient is awaiting a partial hepatectomy. 6 out of 25 patients have died and as yet the median OS has not been reached. We have established a MTD of Ir 180 mg/m^2 d1, Ox 100 mg/m^2 d15 and UFT/LV 250 mg/m^2/day d1–21 of a 28-day cycle. This combination, which provides a high response rate and a