colorectal cancer

**SBCO** MFOLFOX6 + cediranib vs MFOLFOX6 + bevacizumab in previously untreated metastatic colorectal cancer (MCRC): A randomized, double-blind, phase III/II study (HORIZON III)

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Background: Cediranib is a highly potent VEGF signalling inhibitor with activity against all three VEGF receptors. Bevacizumab (bev) is an anti-VEGF-A monoclonal antibody with known clinical benefit in mCRC. HORIZON III compares MFOLFOX6 + cediranib with MFOLFOX6 + bev in patients (pts) with previously untreated mCRC.

Methods: This study had an adaptive Phase II/III design. Eligible pts were randomized 1:1:1 to receive MFOLFOX6 + bev with cediranib (20 or 30 mg/day) or bev (15 mg/kg iv q2w). An independent end of Phase II analysis showed that cediranib 20 mg met all of the predefined criteria for study continuation; subsequent pts were randomized 1:1 to MFOLFOX6 with cediranib 20 mg or bev. The primary objective was to compare progression-free survival (PFS) pre-defined non-inferiority limit upper 95% CI for hazard ratio (HR) <-1.2. Secondary endpoints included overall survival (OS), objective response rate (ORR), safety and tolerability.

Results: Between Aug 2006 and Jan 2009, 1422 pts received MFOLFOX6 with cediranib 20 mg (n=709) or bev (n=713). Baseline characteristics were similar in both arms. At data cut-off (Nov 2009), 65% pts had events for the primary PFS analysis and 98% for OS. There was no significant difference between the cediranib and bev arms for PFS (HR=1.10, 95% CI 0.97, 1.25; P=0.119; median=9.9 vs 10.3 months), but a lower dose intensity after 3 months from chemotherapy dosing between the arms; patients in the cediranib arm received fewer cycles (median 10 vs 12) and a lower dose intensity after 3 months from randomization.

Conclusions: There was no statistically significant difference in PFS, OS or ORR for cediranib + MFOLFOX6 vs bev + MFOLFOX6, however, the predefined boundary for PFS non-inferiority was not met. The safety profile of cediranib was consistent with previous studies, although there was a higher incidence of common AEs with cediranib + MFOLFOX6 than bev + MFOLFOX6.

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**SBDP** Trial participation in a multicentre phase III trial (CAIRO) in advanced colorectal cancer (ACC) patients (pts) in the Netherlands, and a comparison of outcome between trial and non-trial pts

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Background: There is general consensus that progress in cancer research is hampered by a low accrual rate of pts in clinical trials. Trial participation of pts has been estimated between 2-10%, with in some studies 10-15% for potentially eligible pts. Efforts for improvement are often accompanied by the argument that treatment within a clinical trial may result in a better outcome compared with off-study treatment.

Methods: As of January 2003, 820 ACC pts were included in 2 years in the CAIRO trial in the Dutch Colorectal Cancer Group. This trial investigated the optimal use of approved cytotoxic drugs, with entry criteria that also apply to the use of these drugs in general practice. Trial participation was compared with data from the Netherlands Cancer Registry (NCR), which registers all patients at primary diagnosis. Therefore metastatic pts are only registered when they present with stage IV. Non-trial pts who were registered by NCR during the trial accrual period in 29 randomly selected hospitals were checked for CAIRO eligibility criteria, and outcome of non-trial pts who fulfilled these criteria was compared with trial pts.

Results: Of the 803 eligible CAIRO pts, 400 had stage IV disease at diagnosis. During the accrual period, NCR registered 420 stage IV ACC pts of whom 19% received chemotherapy. Thus, trial participation of stage IV ACC pts was 20%. 219 out of 433 NCR-identified pts that received chemotherapy in the selected 29 hospitals would have been eligible but were not included in the CAIRO study and had comparable baseline characteristics compared with trial pts. Trial participation in these 29 hospitals was 39%. Overall survival of eligible non-trial pts was comparable to trial pts (HR 0.99, p=0.7). Non-eligible non-trial pts had a significantly worse outcome.

Conclusion: In this retrospective analysis, using a large multicentre chemotherapy trial in ACC as a reference, we demonstrate that a trial participation of 39% is feasible. Our results also indicate that trial results may be extrapolated to general practice provided that eligibility criteria are observed. These results may serve as a landmark for future studies.

Disclosure: All authors have declared no conflicts of interest.

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**SBDP** Cetuximab plus XELIRI versus cetuximab plus XELOX as first-line treatment for patients with metastatic colorectal cancer (MCRC): Analysis of the randomized trial of the German AIO CRC study group: KRK-0204

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Introduction: Cetuximab combined with 5-fluorouracil/folinic acid plus irinotecan has shown activity in the treatment of mCRC. This randomized phase II trial investigated the efficacy and safety of the epidermal growth factor receptor antibody cetuximab combined with the oral fluoropyrimidine capecitabine plus irinotecan (XELIRI) or oxaliplatin (XELOX) in the first-line treatment of mCRC.

Methods: A total of 185 MCRC pts were randomised to cetuximab (400mg/m² day 1, followed by 250mg/m² weekly) plus XELIRI (irinotecan 200mg/m², day 1; capcitabine 800mg/m² twice daily days 1-14, every 3 weeks; 20% dose reduction of both agents for patients older than 65 years) or cetuximab plus XELOX (oxaliplatin 130mg/m² day 1; capcitabine 1000mg/m² twice daily days 1-14, every three weeks). The primary study endpoint was objective response rate (ORR). KRAS (wild-type or mutant) on codons 12/13/61/146 and BRAF mutation status was determined using a mutation-specific quantitative PCR-based assay.

Results: In the intention-to-treat patient population (n=177), ORR was 47.2% (95% CI: 36.5-58.1) versus 47.7% (95% CI: 37-58.7) and the disease control rate 74.2% versus 77.3% for cetuximab plus XELIRI versus cetuximab plus XELOX. Time to progression and overall survival were 6.4 and 25.5 months for cetuximab and XELIRI compared to 8.2 and 25.3 months for cetuximab and XELOX. Determination of KRAS status was possible in 94.6% of patients. Minor differences were observed in median progression-free survival (PFS) between the two arms (13.7 months for XELOX vs 14.0 months for XELIRI, HR=1.04 [95% CI: 0.80-1.35], p=0.77). The incidence of grade 3/4 adverse events was similar in both arms (86% for XELOX vs 83% for XELIRI).

Conclusion: Cetuximab plus XELOX is as effective as cetuximab plus XELIRI in the first line treatment of mCRC, showing similar median overall survival and similar rates of grade 3/4 toxicity.

Disclosure: All authors have declared no conflicts of interest.

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in 78.3% of patients (n=139). 61.2% of those patients showed a KRAS wild-type, and 38.8% a mutated KRAS status. No differences regarding ORR, DCR, OS or IRR were observed in WT KRAS-like compared to KRAS mutated patients. Both study treatments had manageable tolerability profiles and were safe. The most common grade 3/4 toxicities in the chemotherapy combined with XELOX or XELOX arm were diarrhoea (15.7% versus 19.3%), neutropenia-induced febrile neutropenia (13.5% versus 20.5%), and sensory neurotoxicity (1.1% versus 14.8%).

Conclusion: This randomized trial demonstrated the efficacy and tolerability of cetuximab combined with XELOX or XELOX for the first-line treatment of patients with mCRC, while KRAS mutation status was not predictive of treatment outcome. Disclosure: All authors have declared no conflicts of interest.

EFFICACY AND SAFETY OF SECOND-LINE TREATMENT WITH PANITUMUMAB PLUS IRINOTECAN, BOTH GIVEN Q3W AS SECOND-LINE TREATMENT FOR mCRC PTS. K-RAS ARM STUDY (CLINICALTRIALS.GOV IDENTIFIER NCT00475293) EVALUATES THE EFFICACY AND SAFETY OF PANITUMUMAB (Pmab) HAS DEMONSTRATED EFFICACY AND A MANAGEABLE TOXICITY PROFILE AS AN ADJUVANT TREATMENT IN COLORECTAL CANCER PATIENTS WITH NO M.V.

Methods: Recruit only WT K-RAS tumors when 44 pts were already included of Pmab plus Irinotecan (Iri) given Q3W as second-line treatment for mCRC pts. K-RAS arm study (clinicaltrials.gov identifier NCT00475293) evaluates the efficacy and safety of the Pmab and Iri combination both administered Q3W as second-line treatment for mCRC pts. K-RAS status as a negative predictive marker for Pmab efficacy was not established by the time the trial was planned and started. A protocol amendment was performed to recruit only WT K-RAS tumors when 44 pts were already included.

Results: A total of 85 pts have been enrolled in the study. This analysis was performed on an intention-to-treat basis in the subset of pts with WT K-RAS tumour (53 pts) Pts characteristics: 66 men, median age 67 years (range 37–83), and 90.6% ECOG 0–1, OBR was 22.6% (95% CI 13.3–32.0) and median time duration of response was 4.3 months (range 2.5–15.0). DCR was 64.1% (95%CI 48.9-79.3). Median PFS and OS were 14.3 months and 22 months (95%CI 14.2–24.5) respectively. Most common grade 3/4 related AEs were diarrhea (35.8%), acne-like rash (32.1%), asthenia (18.9%) and neutropenia (18.9%). Two treatment related deaths were reported (gastric ileus and sudden death).

Discussion: From our knowledge this is the first time to show the promising activity of a monoclonal antibody in the treatment of mCRC in pts with WT K-RAS tumours. Results from the second-line treatment line in WT K-RAS mCRC pts. for the whole cohort. The trend towards improved OS for the WT group may be explained with the number of EGFR based regimen in subsequent treatment lines. The capox-bevacizumab regimen, no difference was observed between WT and MT pts. These findings are in line with the reports from the IFL-bevacizumab regimen (Ince, JNCI 2005; Hurwitz, ASCO 2007). In the capri-bevacizumab treated group, PFS and OS in WT and MT was 12.1ms and 12.7ms, respectively (p=0.89) while OS in WT and MT was 28 ms and 25ms in the capri-bevacizumab group, respectively (p=0.88).

Conclusion: We found no significant difference in PFS or OS between WT and MT K-RAS mCRC pts. for the whole cohort. The trend towards improved OS for the WT group may be explained with the number of EGFR based regimen in subsequent treatment lines. The capox-bevacizumab regimen, no difference was observed between WT and MT pts. These findings are in line with the reports from the IFL-bevacizumab regimen (Ince, JNCI 2005; Hurwitz, ASCO 2007). In the capri-bevacizumab treated group, PFS and OS in WT and MT was 12.1ms and 12.7ms, respectively (p=0.89) while OS in WT and MT was 28 ms and 25ms in the capri-bevacizumab group, respectively (p=0.88).


THE MULTI-TARGETED KINASE INHIBITOR AEE788 EXERTS ANTI-ProliferATIVE EFFECTS IN BRAF MUTATED COLORECTAL CANCER CELLS

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Background/Aims: EGFR-KRAS-BRAF signaling system is essential for the establishment and maintenance of cancer cells. BRAF is a downstream molecule from EGFR, EGFR-KRAS-BRAF signaling system is essential for the establishment and maintenance of cancer cells. BRAF is a downstream molecule from EGFR. Cancer patients with tumours harboring a mutation in the KRAS or BRAF genes do not derive benefit from the administration of epidermal growth factor receptor (EGFR)-directed monoclonal antibodies, such as cetuximab or panitumumab. Therefore, other targeted therapies are needed. AEE788 is a novel synthesized oral small-molecule multi-targeted kinase inhibitor with potent inhibitory activity against both EGFR and vascular endothelial growth factor receptor (VEGFR). The aim of this study was to determine the efficacy of AEE788 to inhibit cell proliferation in colorectal cancer cells with different RAS/BRAF mutational status, and to explore the involved mechanisms.

Methodology: The human colorectal cancer cell lines SW48 (KRAS/KRA non-mutated), Caco-2 (BRAF V600E) and HCT-116 (KRAS G13D) were treated with AEE788, in the presence or the absence of EGFR or VEGF. Cell proliferation was measured using an XTT assay. The expression of p21, p27, p16, cyclin D1, c-myc, Bcl-2, Bax and the ratio of Bax/Bcl-2 were assessed by Western blot. The expression of p53, p21, bax, bcl-2 was assessed by Western blot. AEE788 treatment resulted in significant cell death in SW48 and Caco-2 cells, but not in HCT-116 cells. Significant.
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AEE788 reduced the VEGF-dependent cell proliferation of Caco-2, but not of SW584 or HCT-116 cells. These antiproliferative effects were associated with reduced activation of the EGF/R/VEGFR downstream kinases Akt and ERK1/2 only in Caco-2 cells. **Conclusions:** AEE788 exerts anti-proliferative effects in IBRF mutated colorectal cancer cells, by inhibiting both EGF- and VEGF-induced cell proliferation. Our results support AEE788 to be effective in the management of colorectal cancer in a non-mutated KRAS setting, independently of Braf mutational status.

**Disclosure:** All authors have declared no conflicts of interest.

**HIGH THROUGHPUT SOMATIC PROFILING OF THE RAS-RAF-MAP AND PI3K-PTEN PATHWAYS IN ADVANCED COLORECTAL CANCER AND CORRELATIONS WITH RESPONSE TO CETUXIMAB**

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Response to treatment of colorectal cancer (CRC) is influenced by each tumour’s somatic genetic profile. For example, certain subtypes of CRCs show activated EGFR, which has proven efficacy in Kras wild-type tumours but is in general ineffective against K-ras mutant tumours. We developed multi-plexed Sequenom assays for somatic profiling of codons 12, 13 and 61 of K-ras and codon 600 of B-raf. Both assays detected low levels of mutant alleles (~4%), had 99.12% (8642/8719) and 98.14% (1319/1344) genotype concordance for K-ras and B-raf mutations, respectively and high genotype success rates (95.3% for Sequenom vs 92.5% for Pyrosequencing). Three multiplexed Sequenom assays allowed high-throughput screening for additional somatic mutations within the Ras-Raf-MAP kinase and PI3K-PTEN-akt pathways (codons 594 of B-raf, 12 and 13 of K-ras and 454, 545, 645, 1047 of PIK3CA). In total, we screened 1,976 CRCs from patients on the COIN trial (SIRC27288448) and found thirteen different K-ras mutations in a total of 42.27% of CRCs, two B-raf mutations in 9.01% of CRCs, four N-ras mutations in 3.56% of CRCs and five PIK3CA mutations in 12.81% of CRCs. We have previously shown that the addition of cetuximab improves progression free survival (PFS) in patients with K-ras, B-raf and N-ras wild-type tumours, where the partner chemotherapies was Oxaliplatin and when disease extent was limited to 0 or 1 metasis sites (HR=0.73, p=0.04). Here, we analysed individual somatic mutations with respect to whether response to cetuximab. We observed some interesting differences including a trend toward favourable response (PFS) to cetuximab in patients with K-ras G12V CRC (HR=0.92, n=141 patients, and HR=0.78 for those 35 patients treated with Oxaliplatin). However, the individual groups did not reach statistical significance and therefore warrant further investigation in additional cohorts. In collaboration with the COIN Collaborative Group.

**Disclosure:** All authors have declared no conflicts of interest.

**ONCOLOGIC AND FUNCTIONAL OUTCOMES AFTER PREOPERATIVE CHEMORADIOTHERAPY FOLLOWED BY INTERSTITIAL RADIOTHERAPY RESECTION FOR VERY LOW RECTAL CANCER**

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**Purpose:** We conducted a prospective single-institutional study of preoperative chemoradiation therapy (CRT) followed by interstitial radiotherapy resection (ISR), and compared the oncologic and functional outcomes with those treated by ISR alone for very low rectal cancer.

**Methods:** December 1999 and May 2007, a total of 144 patients with very low rectal cancer have been treated using ISR. All patients have completed their three-year follow-ups. Of these patients, one group of 46 had preoperative CRT from 2001 to 2005, followed by the ISR procedure. This groups regimen of preoperative CRT was a total dose of 45 Gy and a continuous infusion of 5FU with a total dose of 2000mg per week, and resection was performed two weeks later. The second group of 98 patients were treated with ISR alone. We compared the disease-free survival rates and local recurrence rates and evaluated the effect on functional by preoperative CRT plus ISR. The risk factors for local recurrence were also analyzed.

**Results:** There were no differences in gender, age, operative procedures, c-stage and follow-up terms among the two groups. The 3-year DFS was not different between two groups (CRT+ISR 72%/68%, P=0.55). There was no significant difference in the 3-year cumulative incidence local recurrence (8%/16%, P=0.19). In the univariate analysis, poor anal function was significantly associated with male and with preoperative CRT. In the multivariate analysis, preoperative CRT was the only independent factor associated with poor anal function after ISR (odds ratio=8.2, 99%CI, 2.3-26.5). Rectal margin of less than 1mm was identified to be the independent risk factor for local recurrence after ISR. In patients with radial margin of less than 1mm, local recurrence rate after preoperative CRT-ISR showed 16% and that after ISR alone showed 41%.

**Conclusions:** When ISR was performed for very low rectal cancer, an addition of preoperative CRT did not clearly lead to a significant reduction of local recurrence. However, preoperative CRT was found to be the factor most strongly associated with poor anal function. When performing ISR, preoperative CRT should be added in only patients who had a high risks of local recurrence.

**Disclosure:** All authors have declared no conflicts of interest.

**INTEGRATIVE EVALUATION OF EGFR DOWNSTREAM SIGNALING FUNCTIONALITY TO PREDICT RESPONSE TO ANTI-EGFR MONOCLONAL ANTIBODIES IN KRAS WILD-TYPE MCRC**

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**Background:** KRAS mutational status was shown to be a highly predictive marker for tumour response to anti-EGFR monoclonal antibodies (cetuximab, panitumumab) in metastatic colorectal cancer (mCRC). However, KRAS status has a poor negative predictive value (NPV), which clearly suggests that additional mechanisms of resistance to EGFR inhibitors exist. Therefore, additional biomarkers are needed to further optimise the selection of KRAS wild-type patients for personalized targeted therapy.

**Methods:** 45 patients (mean age: 61.4 years) with histologically proven metastatic colorectal adenocarcinoma were treated with either cetuximab or panitumumab. KRAS mutations were detected in 23 (51%) patients. In the 22 KRAS wild-type patients, the expression of signaling phosphoproteins belonging to Ras/Raf/Mapk pathway (pErk1/2, pErk1/2, p90RSK6) and PI3K/Akt pathway (pAKT, pGSK3p, p70S6K) as well as pF8MAPK and pEGFR were retrospectively analyzed using phosphoprotein array. KRAS wild-type patients were blindly classified as responders (complete response or partial response) or non responders (stable disease or progressive disease) using principal component analysis (PCA) based on phosphoprotein expression, followed by a linear discrimination analysis (LDA). Quality of classification was assessed by the leave-one-out method.

**Results:** As compared with KRAS status, PCA of phosphoprotein data had a higher sensitivity (97 vs 68%) and NPV (88 vs 58%), but lower specificity (73 vs
Background: According to European Medicines Agency, evaluation of EGFR status by immunohistochemistry is mandatory before treating metastatic colorectal cancer (mCRC) patients with Cetuximab. However EGFR status may depend on the detection methods and may be different in primary and metastatic samples of the same tumor. Furthermore patients with EGFR negative CRC may respond to Cetuximab. Thus many oncologists do not consider EGFR as relevant before Cetuximab therapy in KRAS non mutated mCRC patients. The present study aimed to determine the reproducibility of EGFR status evaluation.

Methods: EGFR status was assessed on the first 74 consecutive samples received for the central review of patients enrolled in the PETACC study. This clinical trial involves patients with stage III colon adenocarcinomas from 8 European countries (EU-20547, EUDRACT-2005-003483-23). EGFR expression was assessed centrally using the FDA approved Dako EGFR pharmDX kit. The 74 slides were analyzed independently by three pathologists (CJ, FPL, SL), expert in digestive pathology and with a long experience in EGFR evaluation, without knowledge of other interpretations. Tumors were considered as positive when at least one tumor cell was stained. The Kappa coefficient (3 raters) was used to explore inter pathologist agreement.

Results: The 74 slides were all considered as good for evaluation by the 3 pathologists. The 3 interpretations were concordant in 58 cases (78%), with 93% positive and 7% negative tumors. The number of positive tumors according to each of the 3 pathologists were 58 (78%), 60 (81%), and 70 (95%), respectively. The number of non-concordant cases compared to the two other pathologists were 6 (8%), 4 (5%) and 6 (8%) for each pathologist, respectively. Inter-observer reproducibility kappa coefficient was 0.44 for negative/positive evaluation.

Conclusion: This work shows that inter-observer reproducibility among expert pathologists for EGFR status reading in CRC is low. Discrepancies are seen in more than 20% of the patients. Our results provide additional arguments not to use this test for KRAS non mutated mCRC patients. The first clinical results show that, for FNP, objective response (21.3%) and survival rate (44.3%) were higher than in patients with positive expression. However the low reproducibility shown in this study might explain the lack of interest of EGFR status in the management of patients treated with Cetuximab and other anti-EGFR agents. In conclusion, before using EGFR inhibition in mCRC, it is mandatory to identify patients who are more likely to respond to this therapy and to acquire reliable data regarding the best strategies to achieve this. The approach should be based on large randomized trials evaluating the benefits of anti-EGFR drugs in patients with specific molecular profiles.

Disclosure: All authors have declared no conflicts of interest.
Background: The efficacy of anti-EGFR therapy in metastatic colorectal cancer is limited to patients with KRAS wild-type tumours. KRAS mutation analysis is therefore assessed prior to the initiation of this treatment, and is usually performed on primary tumour tissue. However, only limited data is available on the concordance of this test between primary tumour and corresponding metastases. We assessed the concordance in KRAS mutation status in an adequately powered study of 309 primary colorectal carcinomas and their corresponding liver metastases.

Patients and methods: Patients with histologically confirmed colorectal cancer who underwent surgical resection of the primary tumour and biopsy or surgical resection of the corresponding liver metastases in three Dutch hospitals were included. Each specimen was subjected to macroscopic dissection, DNA extraction and KRAS mutation analysis. Results: A total of 309 matched samples had a KRAS mutation (35.7%). In 9 cases (3.5%) we found discordance between primary tumour and metastasis; in 5 cases the primary tumour matched samples had a KRAS mutation (35.7%). In 9 cases (3.5%) we found that primary tumour and metastasis had a different KRAS mutation.

Conclusion: We found a high concordance of KRAS mutation status of 96.5% in primary colorectal carcinomas and their corresponding liver metastases. Therefore both primary tumours and metastases can be used for KRAS mutation analysis. Updated results on 309 patients will be presented at the meeting.

Disclosure: All authors have declared no conflicts of interest.

EVALUATION OF KRAS, BRAF AND PI3KCA IN SYNONYMOUS AND METACHRONOUS METASTATIC COLORECTAL CANCER (MCRC)

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Background: The treatment study for MCRC must be based on the evaluation of the EGFR pathway mutational status. Aim of study was to evaluate the incidence of KRAS, BRAF and PI3KCA mutations in synchronous and metachronous MCRC and correlations with metastatic sites.

Methods: Consecutive patients (pts) with MCRC treated at the Oncology Unit of S.Orsola-Malpighi Hospital - Bologna, Italy, between January 2009 and April 2010 were submitted to KRAS, BRAF and PI3KCA mutations analyses. Mutational status analyses were performed in primary tumor or metastasis (mts) and centralised in 1 molecular biology laboratory. Genomic DNA was extracted from highly enriched paraffin-embedded tumor specimens. The status of KRAS (exon 2), BRAF (exon 15), and PI3KCA (exon 9/20) was ascertained by PCR amplification followed by direct sequencing.

Results: A total of 88 pts were evaluated (69 for PI3KCA). Pts characteristics: 54 (61.4%) M and 34 (38.6%) F; 60 (68.2%) of 88; 28 (31.8%); rectum; 49 (55.7%) mts synchronous and 39 (44.3%) metachronous; 36 (40.9%) only liver mts and 62 (59.1%) multiple sites mts. Determinations were performed in 68 (77.3%) primary tumors and 20 (22.7%) tumor mts. Mutational status: 47 (53.4%) KRAS-wt, 41 (46.6%) KRAS-m; 80 (90.9%) BRAF-wt and 8 (9.1%) BRAF-m; 84 (95.5%) PI3KCA-wt and 5 (5.8%) PI3KCA-m. Colon tumors had 34 (35.4%) KRAS-wt and 26 (40.3%) KRAS-m; rectal tumors had 13 (46.5%) KRAS-wt and 15 (53.4%) KRAS-m; Significant difference in KRAS mutation incidence was observed in pts with liver mts alone, 14 (38.9%), as compared with multiple visceral mts 27 (52%) (p 0.028). We observed KRAS-m in 25 (31%) pts with synchronous metastasis vs. 16 (41%) in metachronous (p 0.393). KRAS-m status in pts with synchronous/early metachronous mts (512 months from diagnosis) was 29 (46.8%) compared with 12 (46%) in late metachronous mts (p 0.958). Ten out of 12 (83.3%) pts with BRAF/PI3KCA mutations had synchronous mts at diagnosis.

Conclusions: Our results agree that KRAS is not a prognostic factor. No differences in KRAS mutational status were found between patients with synchronous and metachronous mts, and between liver and visceral multiple mts. A high percentage of BRAF/PI3KCA mutations was observed in synchronous mts.

Disclosure: All authors have declared no conflicts of interest.

KRAS MUTATIONAL STATUS IN JAPANESE PATIENTS WITH COLORECTAL CANCER: RESULTS FROM A MULTICENTER, CROSS-SECTIONAL, LARGE OBSERVATIONAL STUDY CONDUCTED BY THE JAPAN STUDY GROUP OF KRAS MUTATION IN COLORECTAL CANCER

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Background: The KRAS mutation mainly located in the codon 12 and 13 in colorectal tumors indicates unresponsiveness of patients with metastatic colorectal cancer (CRC) to anti-epidermal growth factor receptor (EGFR) antibodies. Various studies have reported that approximately 30–40% of CRC patients have KRAS mutations. However, the data on the frequency of KRAS mutation in Japanese CRC patients is limited to small sample size series. Objective: We aimed to elucidate KRAS mutational status in Japanese CRC patients in this multicenter, cross-sectional, observational study.

Methods: The key eligibility criteria included histologically confirmed colorectal adenocarcinoma with adequate tumor samples. Formalin-fixed paraffin-embedded tumor blocks or thinly sliced tumor sections from 389 centers were sent to commercial laboratories. Almost all KRAS point mutations in the codon 12 and 13 were investigated by direct sequencing.

Results: Between Oct. 2009 and Mar. 2010, 5,887 tumor samples were registered. As of the cut-off date, Apr. 2010, we have determined the KRAS mutational status of 3,688 samples (96%). The median age of patients was 65 years old; 56% were male. The primary tumor site was right colon, left colon, and rectum in 30, 38, and 32% patients, respectively; 92% were obtained from the primary site and 94% were surgically resected samples. The TNM stage at the time of sample collection was stage I, II, III, IV, and recurrence in 2.8, 14, 51, 49, and 2.7%, respectively; 96% were analyzed by direct sequencing. The frequency of KRAS mutation was 37.5% (2126/5668), and 80% (1691/2186) mutations were located in the codon 12.

Conclusion: This is the largest observational study of KRAS mutational status in CRC in Japan. The frequency of KRAS mutations in Japanese CRC patients is similar to those reported in previous studies from western countries. The latest data and the association between KRAS mutational status and baseline characteristics will be reported at the meeting.

Disclosure: All authors have declared no conflicts of interest.

EARLY TUMOR SHRINKAGE FOR THE PREDICTION OF EFFICACY OF CETUXIMAB IN METASTATIC COLORECTAL CANCER (MCRC): ANALYSIS FROM THE CRYSTAL STUDY

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Background: We have shown that early tumor shrinkage predicts long term outcome in colorectal mCRC treated with cetuximab monotherapy or in combination with chemotherapy (CT) in both unselected (BOND trial; Pesseux et al Ann Oncol 2009) and selected (KRAS wild-type [wt]) patients (p1003 De Bock et al, Ann Oncol 2008). Thus early tumor shrinkage may be a hallmark of efficacy of EGFR inhibition and could be used as an on treatment marker of efficacy. In contrast in the AVF1307 and N9741 trial, early tumor shrinkage was not predictive of the outcome benefit from standard CT or the addition of bevacizumab (Grothey et al J Clin Oncol 2008). The CRYSTAL study data show that adding cetuximab to FOLFIRI significantly improves overall survival (OS) (Hazard ratio [HR] 0.796; p=0.0099) in pts with KRAS wt tumors. In this present analysis we investigated tumor shrinkage at first evaluation as a predictor of long term outcome in KRAS wt pts from this study.

Methods: Based on the n-th weekly radiological assessments (RX) reported by the investigator and reviewed by an independent review committee (IRC), relative changes in tumor size from baseline were computed. Kaplan-Meier curves were computed for progression-free survival (PFS) and OS, stratified by treatment and KRAS status.

Results: A sensitivity analysis identified the best cut-off to use as a predictive variable for outcome to be a >20% RX decrease in tumor shrinkage) at week 8. Early tumor shrinkage was associated with a significantly better OS and PFS in KRAS wt pts receiving cetuximab plus FOLFIRI, but not for OS in FOLFIRI treated pts (test for treatment interaction p=0.032 and P=0.001 respectively) (Table).
Background: It has recently been demonstrated in a pooled analysis of data from the CRYS- TAL and OPUS trials, that cetuximab significantly improves the overall survival (OS), progression free survival (PFS) and response rates when added to 1-st line treatment in patients (pts) with KRAS wild-type mCRC treated 1st-line with cetuximab plus FOLFIRI. Ongoing analyses including associations with early skin rash will be presented.

Methods: Individual data from KRAS wild-type pts treated in the CRYSTAL (FOLFIRI +/- cetuximab) and OPUS (FOLFOX +/- cetuximab) trials were analyzed for OS, PFS and safety in elderly (>70 years) and younger (<70 years) pts.

Results: In younger pts with or without cetuximab, the median PFS was 10.0 vs 7.7 months and median OS was 23.6 vs 20.2 months. Similar differences were observed in elderly pts with or without cetuximab: PFS was 8.9 vs 7.2 months and OS was 23.3 vs 15.1 months. (Table). There were no differences in the 60-day mortality rates between patients in both age groups treated with or without cetuximab (Table). Grade 3/4 toxicity was increased in both treatment arms for elderly patients, but there was no obvious interaction between age (< 70 yrs vs > 70 yrs) and the differences for treatment toxicity between the arms.

Conclusions: With a cut-off of 70 years, no major interference between age and efficacy of cetuximab in combination with standard chemotherapy or on the differences for toxicity was shown. Further analysis including additional safety and efficacy data is ongoing.

Disclosure: All authors have declared no conflicts of interest.

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clinical trials may have a selection bias caused by an underrepresentation of pts older than 65 years (v) and of an ECOG performance status &gt;1-2. 1. Non-interventional studies (NIS) are a helpful tool to evaluate approved therapies in daily practice in the general patient population. The aim of this subgroup analysis of a German NIS was to evaluate the efficacy and safety profile of cetuximab plus irinotecan in irinotecan pretreated mCRC patients aged &lt; 65 and &gt; 65 years.

Methods: Between 04/2005 and 11/2007 the data of 497 irinotecan-pretreated pts with mCRC (out of 667 pts documented) were entered in the database of this NIS. We analyzed both patient groups applying descriptive statistics and t2- or Fishers exact test. Results: Median age was 66 y (30-88) with 247 and 250 pts of age &lt; 65 and age &gt; 65, respectively. 17.4% and 21.6% of pts in both groups showed an ECOG status of 2. Pts had 1-4 lines of previous chemotherapy: 26% and 17% 1 line, 43% and 43% 2 lines, 19% and 25% 3 lines, and 13% and 15% 4 lines (p=0.55). Severe cetuximab-related toxicity occurred in 2% (6 and 4 pts, respectively). The median duration of any grade of skin reaction (35 d) was in pts age &lt; 65 significant longer (42 d), than in patients age &gt; 65 (31 d) (p=0.04). However, there was a trend towards higher grade (42d2) skin toxicity in pts age &gt; 65. Skin toxicity led to discontinuation of therapy in 2.6% (6 pts in both groups), but in 22% and 31% to a dose modification and in 6% and 11% to a treatment pause. The objective response rates were similar for both groups: 38.1% for age &lt; 65 vs. 36.4% for age &gt; 65 (p=0.57). The rates for secondary resectability of metastases after cetuximab-based therapy were 4.4% for both groups. Time to tumor progression was similar for both age groups: 4 months [range 1.0-19.0] and 5 months [1.6-17.0] (p=0.79).

Conclusion: Cetuximab has a similar efficacy and safety profile for pts age &lt; 65 and &gt; 65 y. Therefore these results add valuable information to the clinical trials.

Disclosure: All authors have declared no conflicts of interest.
Results: The median magnesium basal value showed a statistically significant decrease after the start of cetuximab plus irinotecan anticance treatment (at 28 days, P<0.0001). Patients with an early decrease of magnesium levels >50% compared to the basal level had a higher tumor response rate (55.8% vs 16.7%, p<0.0001), a longer TTP (6.3 vs 3.6, p<0.0001) and a longer median OS (11.0 vs 8.1, p=0.002).

Conclusions: We have shown that early hypomagnesemia could be a predictor of efficacy and outcome in those patients harboring a wild type KRAS status treated with cetuximab + irinotecan. Magnesium circulating level is an easy and economically inexpensive biomarker to routinely and serially be detected in patients cetuximab-treated.

Disclosure: All authors have declared no conflicts of interest.

HYPOMAGNESEMIA RELATED TO ANTI-EGFR MONOCLONAL ANTIBODY THERAPIES: A POOLED ANALYSIS OF RANDOMISED TRIALS.

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Objective: it is well known that the anti-EGFR monoclonal antibodies cetuximab (C) and panitumumab (P) can be responsible for hypomagnesemia (hypoMg). The purpose of this meta-analysis was to determine the risk of all grades and severe grade (3-4) hypoMg in patients treated with C or P in randomised clinical trials.

Methods: studies eligible for this meta-analysis included those in which patients were randomly assigned to receive standard treatment (chemotherapy and/or radiotherapy) combined with C or P versus standard treatment alone. Randomised phase II and III trials were included. The primary end-point of the meta-analysis was risk of all grades and severe hypoMg. The relative risk was calculated for all studies together and each group separately. Secondary end-points were the incidence of hypoMg and its risk according to the site of cancer.

Results: fourteen reports of randomised controlled trials were included for appraisal and data extraction. Two reports were phase II, and 12 were phase III randomised trials. The incidence of hypoMg was 0.17 in the study group (95% CI 0.16-0.19) and 0.03 in the control group (95% CI 0.02-0.039) (p<0.0001). This incidence was 0.138 in P arms and 0.205 in C arms. Overall risk ratio for hypoMg was 5.1. Risk ratios were 11.5 and 3.4 respectively for the P and C arms. Severe diarrhoea afflicting patients in the two P trials could be responsible for the higher rates. Incidence of severe hypoMg was 0.034 and 0.027 respectively, (p<0.0001), for treatment and control arms. In C arms this value was 0.019 and in P arms 0.028 (p for difference 0.046). Overall risk ratio for severe hypoMg was 8.3 being 7.48 for C and 10 for P. Head and neck cancer patients had a lower incidence of hypoMg (0.068).

Conclusion: the present metaanalysis indicates that anti-EGFR therapies increase, significantly, the risk of all grade and severe grade hypoMg. The real clinical significance of this adverse event is unknown. No deaths or severe complications have been reported. Magnesium supplements and drugs to prevent diarrhoea are recommended precautions to be taken in patients at risk for such complications.

Disclosure: All authors have declared no conflicts of interest.

GENETIC POLYMORPHISMS OF THE FCRIIA-FCRIIIA ARE NOT PREDICTIVE OF CLINICAL OUTCOMES AFTER CETUXIMAB BASED CHEMOTHERAPY IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Background: Cetuximab, anti-EGFR monoclonal antibody, is proved to be effective in patients with metastatic colorectal cancer (mCRC), and the KRAS status is a well-known molecular predictive biomarker. The antibody dependent cell-mediated cytotoxicity (ADCC), which is considered to be another action of mechanisms of cetuximab, is mediated by Fcγ receptor (FcγR) on the host immune cells. The FcγR gene polymorphisms have been studied recently as another possible predictive biomarker for cetuximab. This study investigated the clinical relevance of FcγR gene polymorphisms and KRAS status in irinotecan-refractory mCRC patients treated with cetuximab.

Patients and methods: A total of 123 irinotecan-refractory mCRC patients were screened for KRAS mutations (codons 12 and 13) using direct sequencing from paraffin-embedded samples. Gene polymorphisms for FcγRIIA-158V/F and FcγRIIIA-131H/R were analyzed using peripheral blood of 63 and 109 patients, respectively, by PCR amplification and restriction enzyme digestion. In terms of FcγRIIA polymorphisms, FcγRIIA (H/H), (H/R), and (R/R) were found in 57, 47, and 5 patients, respectively. In addition, FcγRIIIA (V/V), (V/F), and (F/F) were found in 5, 21, and 37 patients, respectively. The clinical outcomes were not significantly different according to either FcγRIIA or FcγRIIIA polymorphisms. Likewise, the combined analysis with KRAS status did make no difference on the clinical effect of FcγR polymorphisms.

Conclusion: A KRAS status did influence the clinical outcome of mCRC patients treated with cetuximab, whereas FcγRIIA and FcγRIIIA polymorphisms did not. These results suggest that ADCC mediated by FcγRIIA and FcγRIIIA may not be the major mechanism of activity of cetuximab in mCRC patients.

Disclosure: All authors have declared no conflicts of interest.

CHEMOTHERAPY WITH OR WITHOUT BEVACIZUMAB IN ADVANCED COLORECTAL CANCER: A PHASE III TRIAL

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Abstract Objective: The objective of this Phase III trial was to compare chemotherapy combined with bevacizumab versus chemotherapy alone, in the treatment of patients with advanced colorectal cancer.

Methods: From September 2004 till September 2008, 222 treatment-naïve patients were enrolled and divided into two Arms: 114 Arm A patients were treated with FOLFIRI and/or FOLFOX in combination with bevacizumab and 108 Arm B patients were treated with FOLFIRI and/or FOLFOX without bevacizumab. All patients were stage IV with histologically-confirmed adenocarcinoma.

Results: The median overall survival of Arm A patients was 22.0 months (95% CI 18.1-25.9) and 25.0 months (CI 18.1-31.9) for Arm B patients. There was no statistically significant difference between the two Arms (p value: 0.1391). No statistically significant difference between the two Arms regarding the response rate was observed: partial response, 36.84% and 35.19% for Arms A and B, respectively. Hematologic toxicity did not differ in the comparison of the two Arms. Non-hematologic toxicity in Arm A involved hypertension in 20.27% of the patients, proteinuria in 6.76%, 3 patients experienced hemorrhage and one patient experienced intestinal perforation. None of these side effects were observed in Arm B patients.

Conclusion: No statistically significant difference was observed in median overall survival in patients with advanced colorectal cancer treated with bevacizumab plus a combination therapy (Arm A) and those treated with the combination only, without bevacizumab (Arm B).

Disclosure: All authors have declared no conflicts of interest.
Eligible patients had to have mCRC with a confirmed diagnosis of colorectal cancer. We examined the effectiveness and safety of the IRIS regimen as second-line treatment in patients with advanced, recurrent colorectal cancer (FIRIS trial) is ongoing in Japan. We previously reported that IRIS is very effective as first-line treatment (33rd ESMO in 2008). Bevacizumab, a molecular targeted agent, is positioned as a standard regimen for the treatment of advanced colorectal cancer. We examined the effectiveness and safety of the IRIS regimen combined with bevacizumab.

Methods: Eligible patients had to have mCRC with a confirmed diagnosis of colorectal cancer (ptcs) with a history of prior chemotherapy; 5-140 mg twice daily p.o. was given on days 1-14 and irinotecan 100 mg/m² and bevacizumab 5 mg/kg i.v. were given on days 1 and 15 of a 28-day cycle. The primary endpoint was safety. The secondary endpoints included overall response (OR), progression-free survival (PFS), and overall survival (OS).

Results: The target number of 53 patients was enrolled as of March 2009. The results are reported for 52 patients with evaluable lesions. The clinical characteristics of the patients were as follows. The median age was 63.5 years (range, 48 to 82). The male: female ratio was 3.2. The performance status on the Eastern Cooperative Oncology Group scale was 0. At interim analysis in January 2010, median number of treatment cycles was 8.5 cycles. On safety analysis, the incidence of grade 3 or 4 neutropenia was 25%. The incidence of other grade 3 or 4 adverse reactions were as follows: diarrhea, 15%; anorexia, 4%; stomatitis, 2%; hypertension, 19%; and gastrointestinal perforation, 0%. The overall rate of response was 57.7%. Two patients had complete response. Twenty-eight patients had partial response, 18 had stable disease, none had progressive disease, and 4 were not evaluable. Median progression-free survival and overall survival are accumulated.

Conclusions: Our results suggest that IRIS plus bevacizumab is a well-tolerated, highly effective chemotherapeutic regimen that is easy to administer. The final data will be reported at this meeting.


EFFICACY AND SAFETY OF SECOND-LINE BEVACIZUMAB (BV) PLUS FOLFIRI / FOLFOX IN PATIENTS WITH RECURRENT COLORECTAL CANCER (MCRC) WHO FAILED PRIOR-COMBINATION CHEMOTHERAPY WITHOUT BV: MULTICENTER RETROSPECTIVE 2ND-BV STUDY IN TSUKUBA CANCER CLINICAL TRIAL GROUP (TCTG)

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Background: Second-line BV + FOLFOX after chemotherapy with irinotecan and a fluoropyrimidine significantly prolongs overall survival (OS) and progression-free survival (PFS) in patients (pts) with mCRC (E2200 trial). However, the second-line BV+FOLOX after failure in FOLFOX has not been reported. We studied retrospectively the efficacy and safety of the second-line BV + FOLFOX in pts who failed in prior-combination chemotherapy without BV.

Methods: Patients who received second-line BV + FOLFOX / FOLFIRI between July 2007 and March 2008 were retrospectively included. Tumor response and disease progression were assessed by investigators.

Results: 139 pts were enrolled in 26 institutions. Median age: 62 years, male: 65%, ECOG PS: 72/127%. Metastatic sites: liver (59%) / lung (48%), number of metastatic site: 1 site (47%) / 2 sites (40%) / > 2 (13%). 104 pts were treated with BV+FOLOX after the first-line irinotecan-containing chemotherapy, and 35 pts were treated with BV+FOLOX after the first-line oxaliplatin-containing chemotherapy. Median follow-up was 17.9 months. 89% of pts had disease progression. The mortality rate within 60-days after treatment completion was 6.5%. One treatment-related death (intestinal perforation) was reported in BV+FOLOX group. Pts-related grade 3 adverse events were bleeding (5.0%), hypertension (4.3%), venous thromboembolism (2.2%) and proteinuria (0.7%). Response rate, median PFS, time to treatment failure and OS were 27%, 7.5 months (95%CI: 6.0 – 9.2), 7.2 months and 23.3 months in the BV+FOLOX group, and 31%, 7.4 months (95%CI: 5.9 – 9.0), 7.2 months and 18.5 months in the BV+FOLFOX group, respectively.

Conclusion: BV+FOLFOX showed similar efficacy to BV+FOLOX in second-line chemotherapy, and safety of additional BV with FOLFOX / FOLFIRI were suggested in clinical practice in Japan.

Disclosure: I. Hyodo: Advisory board member of Yakult, Taibo and Chugai Pharmaceutical Company. Corporate-sponsored research of Taibo Pharmaceutical Company. All other authors have declared no conflicts of interest.
Background: Mutations affecting KRAS and BRAF genes are established predictive markers of outcome with anti-EGFR antibodies in advanced CRC. The relevance of these markers for anti-VEGF therapy is controversial. This analysis was performed to assess the predictive and prognostic impact of KRAS and BRAF gene mutation status in patients receiving C +/- B +/- M in the randomised phase III AGITG MAX study.

Methods: DNA was extracted from archival formalin fixed paraffin embedded tumour tissue from 314 (66.7%) of the original 471 patients participating in the study. Mutation status was determined using high resolution melting endpoint PCR and confirmed with direct sequencing (for equivalent KRAS and all BRAF). Mutation status was correlated with efficacy outcomes (RR, PFS and OS). Predictive analyses were undertaken using a test for interaction involving both C v CB and C v CB CT.

Results: Patient demographics and clinical outcomes were comparable between the two tissue study population and the intent to treat population from the primary trial. Mutations in KRAS and BRAF genes were observed in 28.7% and 10.9% of patients respectively. KRAS gene mutation status (WT v MT) had no prognostic impact for PFS (HR 0.89, CI 0.69-1.14) or OS (HR 0.97, CI 0.73-1.28). In contrast BRAF mutation status (WT v MT) was not prognostic for PFS (HR 0.79, CI 0.54-1.16) but was prognostic for OS (HR 0.52, CI 0.35-0.78 p=0.002). Using the comparison of C v CB CT, KRAS gene mutation status was not predictive of the effectiveness of B for PFS or OS (test for interaction p=0.95 and 0.43, respectively). Similarly, BRAF gene mutation status was not predictive of the effectiveness of B for PFS or OS (test for interaction p=0.51 and 0.70, respectively). Similar results were observed with the comparison of C v CB.

Conclusion: KRAS gene mutation status was neither prognostic for OS nor predictive of survival in patients treated with C v CBCT, BRAF gene mutation status was prognostic for OS but was not predictive of outcome with bevacizumab.

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performed the day before (day -1) starting antiangiogenic therapy and at days 90 and 180. The tumor perfusion parameters evaluated were blood flow (BF), blood volume (BV) and capillary permeability surface area (PS).

Results: Tumor blood flow at baseline was inversely associated with patient progression-free survival. Compared with baseline, bevacizumab induced a significant decrease in the estimated parameters BF, BV and PS on days 90 and 180. Mean change in BF was 54%, in BV 35% and PS 59%. Patients with progressive disease had a lower percent decrease in all parameters than those with stable disease or partial response.

Conclusion: CTP allow evaluation of tumour angiogenesis in vivo. Patients with highly vascularized liver metastases as shown by high baseline tumor BF appear to have a worse prognosis than those who do not. Baseline and percent change in BF, BV and PS by CTP scan following bevacizumab administration correlated with clinical outcome.

Disclosure: All authors have declared no conflicts of interest.

A BLINDED PLACEBO (P) CONTROLLED PHASE 1/2 DOSE ESCALATION STUDY (DES) OF BRIVANIB (B), AN ORAL SELECTIVE DUAL INHIBITOR OF FGFR AND VEGF SIGNALING, IN COMBINATION WITH CETUXIMAB (C) AND IRINOTECAN (I) IN PATIENTS (PTS) WITH KRAS WILD TYPE (KWT) ADVANCED OR METASTATIC COLORECTAL CANCER (AMCRC): SAFETY, TOLERABILITY AND PHARMACOKINETICS (PK) FINDINGS


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Background: B has therapeutic potential in a variety of tumors. B+C treatment is currently being tested in phase 3 in refractory amCRC. An innovative phase 1 design was used to determine if adverse events (AEs e.g. thrombosis-related events [TRE]) were higher with B combinations than the background rate.

Methods: A subject-blind, P-controlled phase 1/2 DES of Brivanib (B) in pts with KWT amCRC. A minimum of 4 pts per cohort were treated with B+C and 2 pts per cohort were treated with P+C (PCI). Standard full-dose I (gqw) and C (qw) were combined with escalating doses of B (200, 400, 600, 800 mg) qd.

Results: 28 pts received 200 (6), 400 (8), 600 (10), or 800 (4) mg of BC or PC for a median of 14 weeks (range 1–38). A dose-limiting toxicity (DLT), grade 3 diarrhea, occurred at 600 mg; 2 DLTs occurred at 800 mg (gr 4 neutropenia >7days, gr 3 diarrhea). An unblinded safety review was conducted by the data safety monitoring committee. Blinded safety data are presented here. (regardless of relationship) occurred in 25/28 pts and are consistent with monotherapy toxicities; there was no increase in the rate of DLT. Main toxicities (diarrhea, neutropenia) are I related and similar between P and B arms. A regimen with C, lower dose I (300mg/m2 qw) and 800mg of B is currently being tested to mitigate the observed toxicities. Unblinded safety data and PK data will be presented at the meeting.

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A PHASE II STUDY OF CEDIRANIB IN COMBINATION WITH MFOFOX6 IN JAPANESE PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (CRC)


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Background: Cediranib (AZD2171) is an oral, highly potent inhibitor of all three VEGFRs. Phase I study results showed cediranib 20 or 30 mg + MFOFOX6 was generally well tolerated in Japanese pts with CRC (Yamaguchi et al). This randomized, double-blind, Phase II study assessed the efficacy of cediranib + MFOFOX6 vs MFOFOX6 alone in Japanese pts with previously untreated advanced CRC.

Methods: Eligible pts (≥18 years, measurable disease, PS 0–1, adequate organ function) were randomized to once-daily cediranib (20 or 30 mg) or placebo (P) + MFOFOX6 every 2 weeks (oxaplatin 85 mg/m2 and leucovorin 280 mg/m2, 5-FU 400 mg/m2 bolus and then 2400 mg/m2). Adverse events (AEs) were evaluated according to CTCAE v3.0. The primary objective was to assess progression-free survival (PFS). Secondary objectives included objective response rate (ORR), overall survival (OS) and safety/tolerability.

Results: Between Jan 2008 and Jan 2009, 172 pts (female 38%, PS 0 71%, 82%)) were randomized in this study (n=58, 56 and 58 in the cediranib 20, 30 mg and P arms, respectively). Baseline characteristics were generally balanced across the three arms. For the PFS comparison of 20 mg vs P the HR was 0.7 (0.44–1.11) and P=0.167, which met the criteria of P<0.2 defined in the protocol. The median PFS was improved by 2 months (10.2 vs 8.3 months). Whereas for the PFS comparison of 30 mg of P the HR was 0.82 (0.54–1.13) and P=0.261, which did not meet the criteria. ORR was 35.4%, 69.6% and 57.9% in the 20, 30 mg and P arms, respectively. The median duration of response was 9.2, 6.7 and 7.1 months for 20, 30 mg and P arm respectively. More patients stopped oxaplatin >12 weeks before progression on 30 mg (33%) compared with 20 mg (14%) or P (6%). The incidence of grade 3/4 AEs was 66%, 75% and 36% in the 20, 30 mg and P arms, respectively. AEs leading to discontinuation were higher (72%) in the 30 mg arm vs 7% for 20 mg and 0% for P. Overall, the most common AEs throughout the study were diarrhea and hypertension. No new safety issues were identified.

Conclusions: This study met its primary endpoint for improved PFS for the addition of cediranib 20 mg to MFOFOX6 in Japanese patients with first line CRC with an acceptable tolerability profile.

Disclosure: All authors have declared no conflicts of interest.

PHASE II STUDY OF FIRST-LINE SUNITINIB (SU) IN COMBINATION WITH IRINOTECAN, LEUCOVORIN, AND 5-FLUOROURACIL (5-FU) [FOLFOX] IN JAPANESE PATIENTS (PTS) WITH UNRESECTABLE/METASTATIC COLORECTAL CANCER (MCRC)


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Background: Sunitinib (SU) is a first-line standard treatment for CRC. The oral, multitargeted tyrosine kinase inhibitor SU has shown preliminary single-agent efficacy in previously treated CRC.

Methods: Japanese pts with confirmed unresectable/metastatic CRC with no prior chemotherapy for metastatic disease were enrolled in this phase II, multicentre, open-label, single-arm study. Pts received FOLHRI (irinotecan 180 mg/m2 bolus and then 2400 mg/m2 as a 46-hr infusion) q2w with SU 37.5 mg/day on Schedule 4/2 (4 wks on, 2 wks off), until disease progression or study withdrawal. PFS was the primary endpoint: overall survival (OS), objective response rate (ORR) and safety.

Results: 71 pts (mean age 58 yrs [range 26–78]; 59% male) were enrolled and started a median of 3 (range 1–9) SU cycles. Median dose intensity was 60.4%. To date, 37 pts (52.1%) had objective progression and 1 pt (1.4%) died without progression. Median
Abstracts

PFS was 6.5 months (95% CI, 4.6-9.2) by independent central review and 7.1 months (95% CI, 5.2-8.0) by investigator assessment. Median OS has not yet been reached. ORR was 33.8%/35.2% (24/25 partial responses), and the rate of best response ≥ stable disease was 78.9%/78.9% by independent review and investigator assessment, respectively. Common all-causality adverse events (AEs) were leukopenia (97.1%), neutropenia (95.7%), thrombocytopenia (84.5%), nausea (78.9%), diarhoea (76.1%), decreased appetite (71.8%), fatigue (64.8%), alopecia (62.0%) and vomiting (53.5%). Grade (G) 3/4 AEs, respectively, included leukopenia (57.7%/9.8%), neutropenia (43.3%/49.3%), thrombocytopenia (22.5%/7.0%), lymphopenia (16.9%/1.4%) and febrile neutropenia (22.5%/0%). The study was terminated early due to findings from a concurrent phase III study of SU + FOLFIRI in non-Japanese pts with mCRC.

Conclusions: SU + FOLFIRI showed activity in patients with mCRC but was associated with a high incidence of AEs. Median PFS of SU + FOLFIRI was similar to historic PFS data with FOLFIRI alone in Japanese patients.

Disclosure: A. Tsuji: has had research funding and has been paid honoraria in the two years prior to trial accrual, by an entity that has a commercial interest in the subject matter; T. Denada: has had research funding from Pfizer Inc. T. Satoh: has had research funding from Pfizer Inc. in the two years prior to accrual; M. Yoshida, Y. Nishina, M. Nagase and K. Muro: has had research funding from Pfizer Inc. in the two years prior to this date; T. Kato: has received funding from Pfizer Inc. in the two years prior to this date. Y. Komatsu: has had research funding from Pfizer Inc., Merck Serono, GlaxoSmithKline, Yakult, Taiho Pharmaceutical LTD and Daiichi-Sankyo. All other authors have declared no conflicts of interest.

**SORAFENIB (S) WITH FOLFIRI AS FIRST LINE THERAPY FOR METASTATIC COLORECTAL CANCER (mCRC): A PHASE I STUDY**

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Abstract: Background: FOLFIRI is a standard treatment for mCRC. S has antitumor activity against mCRC. Drug-drug interactions occur between S and irinotecan (I). This study is to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended phase II dose (RP2D) of sorafenib and FOLFIRI combination, safety at the RP2D in an expanded cohort and pharmacokinetics (PK).

Methods: Cohorts of 3-6 patients (pts) with unresectable mCRC receive escalating doses of S and I (1 in a dose reduced within FOLFIRI combination). Starting doses 1 800mg/m2 iv d1, S 200mg po bid continuously, starting d2 (to allow baseline I PK sampling). Dose escalations are based on toxicity observed at the previous dose level (DL1) up to 5 400mg bid and I 160mg/m2. DELT was defined as occurring within the 1st cycle (cy)-2 FOLFIRI treatments over 28 days). I Pks were collected at timepoints on d1 and cy of d1.

Results: 3 cohorts were concluded. Of 10 ECOG PS 0-1 pts (7 men; 3 women; 2 rectal; 8 colon) with median age of 66, 3 discontinued study due to Cyела 1 side effects; 1 G3 toxicity hand-foot syndrome (HFS); neutropenia. Four pts were enrolled in DL1 (pt #1 was not evaluable for DLT and PK), 3 in DL2 (1 800mg/m2, S 600mg) and 3 in DL3 (I 160mg/m2, S 600mg). No pts in the 1st DL had cycle 1 DLT. The most common grade (G) 3 treatment induced adverse events (AEs) were: HFS, leukopenia 70%, anemia 40%, constipation, anorexia, fatigue, diarhoea, nausea, vomiting 30%. The most severe treatment induced AEs were: G4: 1 neutropenia; G3: 6 HFS, 2 neutropenia, 1 diarhoea, hypertension, hypophosphatemia, vomiting. Best objective responses in 9 evaluable pts (pt #10 not yet evaluable) include 5 PR (8+; 7, 6+; 3+ months); 3 SD (3+; 2, 2+ months), and one DP. Results of the PK analysis evaluating the effect of S on kinetic parameters of I and its metabolites, and its correlation with adverse events will be interpreted at the end of the escalation phase.

Conclusions: Combination therapy with S and modified FOLFIRI in these patients was well-tolerated, supporting the potential feasibility of this combination. Anti-tumor activity for the combination has been observed. Accrual continues with a 4th cohort planned. Supported by Bayer Healthcare Pharmaceuticals

Disclosures: J.A. Maroun: Member on Advisory board. Roche Corporate-sponsored research with Roche Honoraria: Roche

All other authors have declared no conflicts of interest.

**ANALYSIS OF PLASMA BIOMARKERS, DCE-MRI, AND KRAS MUTATIONS IN PATIENTS (PTS) WITH ADVANCED COLORECTAL CARCINOMA (CRC) TREATED WITH THE MULTIKINASE INHIBITOR REGORAFENIB**

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Background: Regorafenib is a novel oral multi-targeted kinase inhibitor of angiogenic (VEGFR1-3, Tie2), stromal (PDGFR-β, FGFR), and oncogenic kinases (KIT, RET, RAF). In vivo models, regorafenib has shown a broad spectrum of antitumor activity. Regorafenib showed clinical activity in renal cell carcinoma and in a Phase I CRC study, for which biomarker results are given here. A Phase III study in pts with advanced CRC is ongoing.

Methods: Biomarker analyses presented here are from a Phase I study of regorafenib, given orally in repeating cycles (Cs) of 21 days (d) 0 7 d off, in pts with refractory CRC. Plasma levels of VEGF and soluble VEGF-R2 (sVEGFR-2) were analyzed pre- and post-dose on d 1 and 21 of C 1, predose on d 1 and 21 of C 2 and 3, predose on d 1 of all subsequent Cs, and at the final visit using the relevant quantitative ELISA. DCE-MRI was assessed at screening, on d 2 of C 1, d 21 of C 1 to 4, every 2nd C thereafter, and at final visit. KRAS mutations were analyzed using archival tumor samples and/or plasma samples obtained during the study. Tumor response was evaluated per RECIST.

Results: 38 pts with actively progressing CRC were treated with regorafenib at doses of 60 mg (n=1), 120 mg (n=4), 160 mg (n=26), and 220 mg (n=7) once daily. The IAU(90) of G0-DTPA as measured by DCE-MRI decreased over the course of the study (% change [arithmetic mean] to baseline d 2: -6.7%; d 21: -34.1%; d 49: -37.9%). VEGF plasma levels (change in arithmetic mean) increased by 62.4% (d 21) and 95.6%...
(d 94), aVEGFR decreased by 35.8% (d 21) and 42.8% (d 49). KRAS mutations were found in 19/36 of evaluable pts (53%). Pharmacodynamic changes in DCE-MRI VEGF and aVEGFR-2 were not correlated to PFS. Pts with mutated or wildtype KRAS were equally distributed among those who clinically benefited (PFS 2100 d).

Conclusions: Observed changes in angiogenic plasma cytokines and decrease of tumor blood flow as measured by DCE-MRI are supportive of the antiangiogenic activity of regorafenib in pts with advanced CRC. Althoug the small number of pts analyzed, KRAS status was not predictive for clinical benefit as measured by PFS.

Disclosure: O. Christensen: Employee of Bayer HealthCare Pharmaceuticals

M. Jeffers: Employee of Bayer HealthCare Pharmaceuticals (Bayer is developing Regorafenib)
J. Kratzschmar: Employee of Bayer Schering Pharma AG

All other authors have declared no conflicts of interest.

IDENTIFICATION OF PREDICTIVE BIOMARKERS FOR INDIVIDUAL RESPONSE TO MFOLFOX6 IN COLONIC CANCER PATIENTS

M. Nishiyama1, A.T.C. Chan1, M. Nishiyama: corporate-sponsored research: Yakult Honsha Co. Ltd

values is now going on, along with research for the functional roles of the selected 14 expression levels. microarray analyses demonstrated that another 14 genes including RNF145, PEPD and significantly better in patients with low ERCC2 expression (P=0.039). Furthermore, The therapeutic response was not related to tumoral KRAS mutational status at all, and 234 days, respectively. The most common grade 3/4 toxicities were neutropenia 60.4% (1CR and 28 PRs), and median overall and progression survival were 930 days

Fifty pts received a total of 424 treatment cycles. Overall response rate was
identify novel prediction marker genes closely correlative with response to
GSTP1, EGFR, VEGF, and TNFRSF1B-. Microarray analysis was also performed to
markers of individual response to mFOLFOX6, in terms of efficacy and toxicity.

indicators of individual response to the basic regimens are urgently required.

basic regimens, such as FOLFIRI and FOLFOX, remain unpredictable. Molecular
determination of response to these therapies. Even so, the clinical efficacy and toxicity of the basic regimens, such as FOLFIRI and FOLFOX, remain unpredictable. Molecular indicators of individual response to the basic regimens are urgently required.

Methods: This prospective study was conducted to determine putative predictive markers of individual response to mFOLFOX6, in terms of efficacy and toxicity. Chemo-naive patients with stage IV colorectal cancer were eligible for this trial after palliative operation, and received mFOLFOX6 treatment. Along with KRAS-mutational analysis in tumor, expression analysis in tumor and genotyping were performed for 9 possible marker genes-DPYD, TMY, ERCC1, ERCC2, XRCC1, GSTP1, EGFR, VEGF, and TNFRSF1B-. Microarray analysis was also performed to identify novel prediction marker genes closely correlative with response to mFOLFOX6.

Results: Fifty pts received a total of 424 treatment cycles. Overall response rate was 60.4% (1CR and 28 PRs), and median overall and progression survival were 930 days and 234 days, respectively. The most common grade 3/4 toxicities were neutropenia 60.4% (1CR and 28 PRs), and median overall and progression survival were 930 days

Conclusion: Expression of ERCC2, TMY, and newly identified 14 genes would be predictive for individual response to mFOLFOX6. A study to validate their predictive values is now going on, along with research for the functional roles of the selected 14 genes.

Disclosure: M. Nishiyama: corporate-sponsored research: Yakult Honsha Co. Ltd All other authors have declared no conflicts of interest.

TITLE: INTERMITTENT VERSUS CONTINUOUS ERLOTINIB WITH CONCOMITANT MODIFIED ‘XELOX’ (Q3W) IN FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (mCRC)

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Purpose: Erlotinib (EGFR tyrosine kinase inhibitor, TKI) has promising activity when combined with capecitabine (Xc) and oxaliplatin (Ox) (XELOX) in the 1st line therapy of mCRC. There is no data on relationship between KRAS status and response

to EGFR TKI in mCRC. Preclinical data suggest sequence-dependent synergism between EGFRI TKI and fluoropyrimidines, and vs they thus exhausted the feasibility of combining erlotinib with XELOX in 1st-line therapy of mCRC.

Method: Chinese patients (pts) with untreated mCRC were randomized to Arm A: Continuous-erlotinib (100mg daily, D1-21), Ox 85mg/m(2) bd on D1-14, and Ox 130mg/m(2) D1, q3wk, or Arm B: Intermittent erlotinib 150mg on alternate days on D1-14, then daily from D15-21, with Ox 750mg/m(2) bd on D1-14, and Ox 130mg/m(2) D1), q3wk. Primary endpoint was response rate (RR). Archived tumors were retrieved retrospectively for KRAS analysis.

Result: 58 pts were randomized (29pts in each arm) in a single institution from Nov 2007 to Nov 2009. Baseline characteristics: median age 56 yrs, 63% male, 74% had prior surgery. Both arms had similar characteristics, except more pts in Arm B had prior adjuvant chemotherapy (p=0.02). Overall RR was 86.8% in Arm B (17/20pts) and 41% in Arm A (12/29 pts, p=0.02, chi-square). For drug compliance: median no. of cycles were 5 (Arm A) and 7 (Arm B); no. of pts who had > 8 cycles were 9 (31%, Arm A) and 12 (41%, Arm B), dose interruptions were required in similar no. of pts in Arm A and B. For toxicity: 14 pts (48%) in each arm had Gr 3-4 toxicities. 1 pt in Arm B died of metabolic acidosis from probable abdominal sepsis. Gr 3-4 thrombocytopenia was more common in Arm A (11 pts, 34%) than Arm A (5 pts, 17%). Gr 3-4 sensory neuropathy was more common in Arm B (10pts, 34%) than Arm A (3 pts, 10%).

Conclusion: Preliminary analysis suggests that pts on intermittent erlotinib with XELOX had higher RR and incidence of hyperbilirubinemia and sensory neuropathy.

Data on KRAS status will be presented.

Disclosure: B. Ma: I am on research grant from Novartis and consultancy with AstraZeneca.

All other authors have declared no conflicts of interest.

COST COMPARISON: CAPECITABINE + OXALIPLATIN (XELOX) VS 5-FU/LV + OXALIPLATIN (FOLOX4) IN THE ADJUVANT TREATMENT OF PATIENTS WITH COLON CANCER (ACC)

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Background: FOLOX4 has been the chemotherapy (ctx) of choice for patients with stage III colon cancer. Recently, the international NO16968 study reported results confirming the efficacy of XELOX in this setting, and evidence suggests that both regimens have at least equivalent efficacy. The relative attractiveness of these regimens to providers, patients and payers will depend on medical resource utilization (MRU).

This analysis compared the MRU and related costs required to treat an average aCC patient with either XELOX or FOLOX4 from the Swiss healthcare system perspective.

Method: In the absence of a direct comparison, detailed MRU data collected for XELOX from study NO16968 (aCC) and for FOLOX4 from study NO16966 (metastatic colorectal cancer) were analyzed. Since the FOLOX4 regimen is the same in both indications, MRU data from NO16966 were considered valid proxies for an aCC patient. MRU categories considered were hospitalizations due to adverse events (AEs), ambulatory encounters due to AEs and other reasons, AE medication and central venous access (CVA) placements.Ctx drug and administration costs were considered as per protocol. Unit costs were derived from official tariffs (Spezialita¨ tenliste, Tarmed 2010). Total costs while on treatment (24 weeks) for an average aCC patient with aCC were compared.

Results: The cost comparison shows that XELOX is cost saving vs FOLOX4 with an average cost reduction per patient of CHF 8883. This cost saving is due to the lower administration costs experienced in the XELOX arm through fewer administrations per cycle and longer cycle length (21 vs 14 days) vs FOLFOX4.

All other authors have declared no conflicts of interest.

Disclosure: All other authors have declared no conflicts of interest.

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META-ANALYSIS OF THE VALIDITY OF PROGRESSION-FREE SURVIVAL AS A SURROGATE ENDPOINT FOR OVERALL SURVIVAL IN METASTATIC COLORECTAL CANCER TRIALS

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Background: The validity of progression-free survival (PFS) as a surrogate endpoint for overall survival (OS) in metastatic colorectal cancer (mCRC) trials has been studied extensively, but primarily in first-line treatment (for example, BUSY et al.) in Clin Oncol. 2007;29:5318–5324 and Saad et al. Ann Oncol. 2010;21:7–12. We sought to confirm and extend this research by investigating the influence of such factors as line of therapy on the relationship between OS and PFS in mCRC trials.

Methods: In a systematic literature review, mCRC phase 2 and 3 trials that presented OS and PFS (or time-to-progression) results were eligible. Correlation between these endpoints was estimated by single treatment arm and by study. Treatment effect in each study was defined as the ratio of the median time to event (either OS or PFS) in the two treatment arms. Meta-regression analyses were conducted using least squares meta-regression models weighted by study sample size. Statistically significant factors were used to create subgroup analyses.

Results: A total of 66 articles met the initial search criteria and 62 were included in the analysis (total of 23,527 patients). High positive correlation was found between the regression equation for the relationship between OS and PFS (or time-to-progression) results were eligible. Correlation between these endpoints was estimated by single treatment arm and by study. Treatment effect in each study was defined as the ratio of the median time to event (either OS or PFS) in the two treatment arms. Meta-regression analyses were conducted using least squares meta-regression models weighted by study sample size. Statistically significant factors were used to create subgroup analyses.

Conclusions: OS and PFS (or time-to-progression) results were eligible. Correlation between these endpoints was estimated by single treatment arm and by study. Treatment effect in each study was defined as the ratio of the median time to event (either OS or PFS) in the two treatment arms. Meta-regression analyses were conducted using least squares meta-regression models weighted by study sample size. Statistically significant factors were used to create subgroup analyses.

ANALYSIS OF NEUROSENSORY ADVERSE EVENTS (NSAEs) INDUCED BY FOLFOX4 TREATMENT IN ADVANCED/RECURRENT OR ADJUVANT COLORECTAL CANCER IN ASIAN AND WESTERN PATIENTS (PTS)


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Background: FOLFOX4 is a standard regimen for the treatment of advanced/recurrent and adjuvant colorectal cancer. In order to support Japanese adjuvant indication, NSAEs were evaluated in both Asian and Western Pts in 6 FOLFOX4 studies. Materials and methods: A total of 3359 colorectal cancer Pts, 1515 Asian and 1844 Western, treated by FOLFOX4 were included from 2 Asian [J-PMS (Jpn Post-Marketing Surveillance) and adjuvant MASCOT] and 4 Western [de Gramont et al. 1st line phase III (EC2962), Goldberg et al. 1st line phase III (9741), Rothenberg et al. 2nd line phase III (ECF4584) and adjuvant MOSAC] studies. NSAEs were graded by DEB-NTC (1-PMS), NCI-CTC ver. 1 (ECF2962, MOSAC) or ver. 2 (MASCOT, N9741, EFC4584) scales, re-coded by MedDRA ver 9.0, and analyzed by SAS® ver 8.1.

Results: Pts received FOLFOX4 for 6 - 12 cycles over 16 - 28 weeks. Median dose intensities of L-OHP, bolus and infusion 5-FU varied from 33 - 35.6 - 35.5 – 35.4 mg/m² to 1050 mg/m²/week, respectively. In both populations, NSAE was one of the most frequent grade ≥1 AEs (50.6 - 92.1%), and grade ≥3 AEs were reported in 1.9 - 18.7%. The incidence increased with increase in L-OHP cumulative doses (CD). The CDc, that induced grade ≥3 NSAEs in 10% Pts calculated by Kaplan-Meier method, were higher in Asian Pts (1526 mg/m² and NR) than in Western Pts (805 - 832 mg/m²). All Pts who experienced grade-3 NSAEs in MOSAC recovered to grade 2 or less within 12 months of follow-up, and 96% of grade-3 Pts in MOSAC. Analysis of correlation between NSAEs and demographic/baseline characteristics by Fisher’s exact test and logistic regression showed no significant trend.

Conclusions: There was a trend toward reduced NSAEs (grade ≥3) among Asian Pts as compared with Western Pts.
Conclusion: This study recommends the application of TMA technique for its economic advantage and reliable quick throughput. The results from this study also suggest that overexpression of p53, bcl-2, and her-2/neu protein markers appear to be useful in selecting a group of CRC patients with a worse prognosis and constitute potential candidates for adjuvant therapy.

Disclosure: All authors have declared no conflicts of interest.

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THROMBOCYTOSIS AS A PREDICTIVE AND PROGNOSTIC MARKER IN ADVANCED COLORECTAL CANCER (ACRC): RESULTS OF THE MRC COIN TRIAL EXPLORED.

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Background: Simple and reliable biomarkers for cancer therapy have the potential to make huge differences to individual patient care. COIN randomised 1630 pts. with previously untreated aCRC to continuous (arm A) or intermittent (arm C) chemotherapy. It identified a non-significant difference in OS of 1.5 mths (PPA) in favour of continuous therapy at the expense of 2.3 mths of extra time on therapy. Here we explore sub-group analyses to predict those individuals most likely to benefit from continuous therapy.

Methods: A Cox proportional-hazard model was fitted separately for patient, pathological and biological covariates to predict OS in the PPA population. In each case, a traditional, the predictive factor, and a treatment-predictive factor interaction term were entered into the model. Interaction tests were carried out using likelihood-ratio tests of the null hypothesis that the interaction coefficient is zero.

Results: A baseline platelet level >400/mL identified a group of patients (28%) with worse prognosis and with a significant survival detriment in using intermittent therapy, test for interaction; HR:1.65 (95% CI 1.19 to 2.28), p=0.003. Patients with raised baseline platelets are more likely to be male, <65 yrs, and have WHO PS >1, primary tumour in the colon, unresected primary, synchronous metastases, liver metastases, peripheral metastases. There is an increased incidence of pain and vomiting in those with raised platelets, which appears better controlled on continuous therapy. In Arm A, raised platelet count is significantly associated with increased pain: G1: 66% vs 71% (p=0.282). In Arm C, raised platelet count is not associated with increased pain: G1: 72% vs 80% (p=0.061).

NRAS, KRAS and BRAF mutation status were not associated with platelet level. Further analyses will be presented in terms of biological data QoL and toxicity.

Discussion: This simple routinely performed biomarker can identify a subset of patients who do much less well with intermittent chemotherapy. In contrast, those three quarters of patients in this study with normal platelets at randomisation suffered no loss in overall survival and reaped all the benefits of chemotherapy free intervals.

Disclosure: All authors have declared no conflicts of interest.

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NATURAL HISTORY OF MALIGNANT BONE DISEASE IN COLORECTAL CANCER: FINAL RESULTS OF A LARGE ITALIAN "BONE METASTASES" SURVEY

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Introduction: Bone metastases are an emerging clinical problem in colorectal cancer patients probably related to survival increase. There are no data in literature about the role of BPs in the treatment of bone disease from colorectal cancer. We present the final data of a large Italian multcenter retrospective study.

Methods: 264 colorectal cancer patients with occurrence of bone metastases have been included in the study. All patients were died due to cancer at the moment of the study inclusion. Patient Characteristics, Skeletal Related Events (SRE) data and median survival after bone metastases appearance have been collected in a master data base and statistically analyzed. The primary efficacy endpoint was time to first SRE; secondary endpoint was median survival. 31 patients have been analysed as control group.

Results: In 107 patients bisphosphonates data were not available. A total of 157 patients have included for zolendronic efficacy analysis. A total of 126 patients received zolendronic acid (4 mg) via a 15-minute infusion every 4 weeks until performance status worsening or death. The median time to first SRE in the whole population was 2 mths (1.04 – 3.45). The median time to first SRE in the zolendronic treated patients was 3.16 mths (0.49 – 2.19) compared with 1.71 mths (0.41 – 0.90) in the control group (p: 0.009). The median survival after skeletal progression was 7 mths (5.73 – 8.704). The median survival in the zolendronic treated group was 10 mths (8.08 – 11.91) compared with 6 mths (4.45 – 7.54) (p: 0.161).

Conclusions: complete results of statistical analysis will be presented during the meeting. The present analysis represent the efficacy demonstration of a bisphosphonate in bone metastases from colorectal cancer patients.

Disclosure: All authors have declared no conflicts of interest.

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PRELIMINARY RESULTS FROM THE SOUTH AUSTRALIAN (SA) CLINICAL REGISTRY FOR ADVANCED COLORECTAL CANCER (CRC) ASSESSING THE IMPACT OF AGE AND CHOICE OF CHEMOTHERAPY ON OUTCOME

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Aims: The SA Clinical Registry for Advanced Colorectal Cancer aims to encompass all patients in SA who have been diagnosed with metastatic CRC. In this abstract we report here outcomes, assessing the difference in treatment patterns for those <70 yrs with those >70 yrs and outcome based on initial choice of chemotherapy (CT).

Methods: All patients diagnosed with mCRC after 1/2/2006 were eligible to be included. For the analysis patients receiving CT were assessed by choice of single or combination CT (CC) and by age (<70 yrs and >70 yrs). Disease-specific survival data was assessed using Kaplan-Meier product moment estimates.

Results: 1544 patients with mCRC have been entered. Mean age 71 yrs (range 17.4 – 105.4yrs). 822 (52.6%) patients had some form of CT for mCRC, median age 68 yrs, compared to median age for no CT of 79 yrs (28% of patients >70 yrs and 59% >70 yrs did not receive CT). Of those patients who received CT, the characteristics of those <70 yrs and >70 yrs were well balanced for gender, location of primary, hepatic only

Disclosure: All authors have declared no conflicts of interest.
metastases, and rates of hepatic and lung resection. 81% and 51% of those <70 yrs and >70 yrs respectively received CCT first-line, and 47% and 19% received second-line CCT, while 35% and 11% received third-line CT. 30% of patients <70 yrs received at least one line of treatment containing EGFR or VEGFR targeted therapy and 14% >70 yrs. Median survival of patients <70 yrs and >70 yrs receiving CT was 24.4 months and 20.4 months respectively (p=0.02) and 21.4 months and 24.8 months for those who also received targeted therapy. Median survival for patients receiving first-line single agent fluoropyrimidine was 16 mths (n=249, med age 74yrs) compared to first-line CCT 26 months (n=556, med age 65yrs) (p=0.001, HR 1.74) and using cox regression analysis age was not an independent predictor for survival.

Conclusions: Age appears to impact on the initial CT choice, with the majority of patients <70 yrs receiving first-line CCT whereas nearly 50% of those >70 yrs received single agent therapy. Comorbidity may have impacted on treatment decisions, however, survival appears to be better in those treated with first-line CCT and should still be considered in the older patient.

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All other authors have declared no conflicts of interest.

E33P \textbf{PATIENTS NOT RECEIVING SYSTEMIC THERAPY FOR METASTATIC COLORECTAL CANCER - WHAT ARE THE DRIVERS AND WHAT ARE THE OUTCOMES?}

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Background: Despite major advances in the systemic therapy of metastatic colorectal cancer (mCRC), leading to improved symptom control and life expectancy, some pts still do not receive any treatment. Analyses of this pt population are critical to understanding the reasons that treatment may not be pursued, the appropriateness of this decision and the ultimate impact on survival outcomes.

Methods: We examined a prospective, comprehensive database at 4 hospitals for detail regarding patients diagnosed with mCRC between January 2003 and December 2009, focusing on the patients that were not treated and their survival outcomes.

Results: 445 pts (60% male, 40% female) with metastatic disease were identified. Preliminary analyses revealed that 221 pts (49.6%) had chemotherapy initiated at diagnosis and 62 pts (14%) had later treatment after an initial watch and wait approach. Of the pts that never received treatment, (n=162, 36.4%), for 153 (94%) this decision was made at diagnosis, with only 9 pts (6%) that initially undertook a watch and wait approach never receiving treatment. Pts for whom the decision not to treat was made at diagnosis, were significantly (p < 0.05) older (median age 71.4 yrs vs 63.6 yrs for pts treated immediately) and with a worse performance status (PS) (83.3% ECOG >2 vs 1.61% of treated pts). Sites of disease, presence or absence of symptoms and comorbidity as calculated by the Charlson's index did not significantly impact on treatment decisions. Of the untreated pts, the most frequently documented reason for not undergoing treatment was poor PS (50.8%) followed by comorbidities (41.5%) and/or age (16.7%). Data related to the median survival of untreated versus treated pts will be presented.

Conclusions: A significant proportion of patients with metastatic colorectal cancer do not receive any systematic therapy, a decision that is usually made at the time of diagnosis. Most patients undergoing an initial watch and wait approach are ultimately treated. Poor PS, co-morbidity and advanced age are the dominant reasons that pts do not receive treatment.

Disclosure: All authors have declared no conflicts of interest.

E33P \textbf{SURVIVAL AFTER SURGICAL RESECTION OF HEPATIC METASTASES FROM COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS}

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Purpose: To summarize studies of survival after resection of colorectal cancer liver metastases (CLM).

Methods: We reviewed articles published 1999–2009 in English of studies with ≥1000 patients who underwent liver resections for CLM with ≥24 months of follow-up. This update includes seven additional studies that reported on post-operative mortality and morbidity, health care resource utilization costs, quality of life, and clinical guidelines. Seven prognostic factors of mortality were considered in a meta-analysis: grade, tumor size, extrahepatic disease, number of metastatic sites, number of palliative chemotherapy’s lines and type of the first-line chemotherapy.

Conclusion: Primary tumor resection seems to improve overall survival in patients with synchronous CRC metastases and good performance status. A prospective randomized trial integrating the quality-of-life factor should be organized.

Disclosure: All authors have declared no conflicts of interest.

E31P \textbf{SHOULD THE PRIMARY TUMOR BE RESECTED IN PATIENTS WITH UNRESECTABLE SYNCHRONOUS METASTASIS OF COLORECTAL CANCER? PROGNOSTIC RETROSPECTIVE MULTICENTRIC STUDY OF 128 PATIENTS}

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Introduction: Indication of primary tumor resection remains controversial in patients (pts) with asymptomatic colorectal cancer (CRC) and metastatic synchronous metastasis. The aim of this study was to compare survival of patients with metastatic CRC who underwent elective resection of the primary tumor to those who did not.

Patients and methods: Data of 275 consecutive pts from 5 centres treated with palliative first line chemotherapy for metastatic CRC between June 2004 and June 2008, were retrospectively reviewed. Demographic, clinical, tumor-related, and chemotherapeutic-related variables were collected in 128 pts with synchronous metastases and good performance status (ECOG 0 or 1). Overall survival (OS) was calculated from the first date of infusion of chemotherapy to death or last follow-up. Survival analyses were performed using the Log-Rank test and the Cox Model.

Results: The 128 pts were male in 72% (92/128). Median age was 63 years old (38-88). 67% (86/128) of patients underwent primary resection. Characteristics for pts with tumor’s resection/non-resection are as follow : 66.7% (134/200) vs 71% (43/50) of colonic tumors (p=0.01), 24% (80/342) vs 12% (19/159) of metastatic tumors (p=0.03). No impact of size <5 cm on OS was observed. A significant impact on OS was observed for patients with primary tumor resection (24.8 mths (95% CI[17.3-29.7]) vs 17.5 mths (95% CI[12.5-21.2]) p=0.01). In multivariate analysis, OS was significantly improved for patient with primary tumor resection (HR 2.2; CI 95% [1.3-3.8]; p=0.02) whatever number of metastatic sites, number of palliative chemotherapy’s lines and type of the first-line chemotherapy.

Discussion: Primary tumor resection seems to improve overall survival in patients with synchronous CRC metastases and good performance status. A prospective randomized trial integrating the quality-of-life factor should be organized.

Disclosure: All authors have declared no conflicts of interest.
Annals of Oncology

**RIPK1 POLYMORPHISM AS PROGNOSTIC MARKER FOR SURVIVAL IN PATIENTS WITH COLORECTAL CANCER AFTER COMPLETE RESECTION**

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Since apoptosis plays a key role in cancer progression, the present study analyzed the polymorphisms of apoptosis-related genes and their impact on survival after curative resection in patients with colorectal cancer. Three hundred and ninety-seven patients were enrolled in the present study. The genomic DNA was extracted from fresh colorectal mucosal tissue, and 15 SNPs of 12 apoptosis-related genes determined using a Sequenom MassARRAY system. During the median follow-up of 41.6 (range, 0.7-85.5) months, 80 relapses and 67 deaths occurred. Among the target polymorphisms, FAS rs10788624 and rs8008062 in a recessive model of the minor allele and RIPK1 rs2272990 in a dominant model of the A allele were associated with survival in a log-rank test. Moreover, the GAAA genotype of RIPK1 rs835G>A (rs2272990) was significantly correlated with a worse disease-free and disease-specific survival when compared to the GG genotype (hazard ratio [HR] = 1.810; 95% confidence interval [CI] = 1.108 - 2.959; p=0.018 and HR = 2.372; 95% CI = 1.302 - 4.321; p=0.005, respectively) in a multivariate survival analysis. RIPK1 polymorphism can be considered as a possible prognostic marker for survival after curative resection in patients with colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

**FUFIRI OR MIROX FOR FIRST-LINE TREATMENT IN METASTATIC COLORECTAL CANCER (mCRC) AND SECONDARY RESECTION OF LIVER METASTASIS: A POST-HOC ANALYSIS OF TUMOR RESPONSE AND OVERALL SURVIVAL IN THE FIRE-TRIAL**

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Background: Chemotherapy in metastatic colorectal cancer (mCRC) can downsize colorectal liver metastasis (CLM) for curative secondary resection. We evaluated downsizing and survival of FUFIRI and miRox treatment in non-selected pts in this setting.

Patients and methods: Data from a phase III, randomized, multicenter trial with 479 pts treated with FUFIRI (irinotecan 80 mg/m², 5-FU 2000 mg/m², folinic acid 500 mg/m² weekly) vs miRox (irinotecan 80 mg/m² plus oxaliplatin 85 mg/m² weekly) applied on days 1, 15 and 29 of a 7-week cycle were evaluated. Assessment of the largest hepatic lesion was performed at the time of randomization and before surgery. Resection rates in the subgroup of liver-only pts (248/679, 36.4%) and 15 patients of the miRox arm (6.2%) (p= 0.179). Total resection rate of the study was 7.9% (36/479). R0-resections in 29 cases (18 vs. 11, FUFIRI vs. miRox, p=0.169). Resection rates in the subgroup of liver-only pts (248/679, 36.4%) were 20.2% (FUFIRI) and 11.2% (miRox) (p=0.050). R0-resections 15.8% and 8.2% (p=0.064). In both groups highly significant downsizing of liver metastasis with 33.3% reduction of length, 35.0% reduction in width and 57.6% reduction of surface could be achieved (p<0.001). Mixed model analysis of variance (ANOVA) showed, that R0-resection vs. R1-resection was significantly greater in the FUFIRI group (81% vs 69%, p=0.001). These findings were consistent with results of the liver-only subgroup (87% vs. 67%, p=0.001). Median overall survival (OS) of all 38 resected pts was 45.8 months. One-year-survival and 5-year-survival was 97.4% and 37.1%, respectively. For pts treated by BV in a real-life setting, secondary resection of mCRC for initially unresectable metastases was possible for 19% of pts with 85.7% R0-R1. Evaluation of morbidity and longer follow-up will allow the real long-term benefit to be studied.

Disclosure: All authors have declared no conflicts of interest.

**RISEP**

**ANALYSIS OF OVERALL SURVIVAL AMONG PATIENTS WITH METASTATIC COLORECTAL CANCER, WITH AND WITHOUT UNDERGOING ELECYOTIC COLECTOMY**

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Analysis of overall survival among patients with metastatic colorectal cancer, with and without undergoing elective colectomy

Introduction: Controversy exists regarding the management of metastatic colorectal cancer. Palliative resection of the primary tumor has become established for patients presenting uncontrollable bleeding, total intestinal obstruction or perforation. The real benefit from resecting the primary tumor in asymptomatic patients remains undefined.

Objectives: Evaluate overall survival among patients with metastatic colorectal cancer who underwent elective surgery to resect the primary tumor, in comparison with patients who did not undergo this procedure, along with their prognostic, demographic and clinical factors.

Methods: Retrospective cohort study in which 203 patients with metastatic colorectal cancer at Barretos Hospital. Demographic, clinical and treatment variables were gathered. Descriptive analysis was performed on the data. For the survival analysis, the Kaplan-Meier product-limit estimator was used. To compare the curves, the log-rank test was used. Variations that presented descriptive levels lower than 20% were entered into the Cox multiple regression model.

Results: The 12-month overall survival (OS) among the patients who underwent elective colectomy was 66.4%, 36-month OS was 26.4% and 60-month OS was 16.2%. The patients who did not undergo surgery had a 12-month OS of 25.1%, 36-OS of 1.3% and 60-month OS of 1.3% (p<0.001). Independent prognostic factors were: not undergoing the colectomy procedure; not undergoing resection of metastasis; and not undergoing chemotherapy, adjusted according to the patients’ performance status.

Conclusion: The results from our study suggest that asymptomatic metastatic patients who underwent elective colectomy presented favorable outcomes with greater overall survival. The other independent factors that led to a better prognosis were resection of the metastatic disease and implementation of chemotherapy, adjusted for good clinical conditions (performance status). The benefit regarding survival was directly proportional to the number of treatments that patients were able to undergo.

Disclosure: All authors have declared no conflicts of interest.

**RESECTION OF COLORECTAL CANCER (CRC) METASTASES AFTER BEVACIZUMAB (BV) TREATMENT: RESULTS OF THE ETNA COHORT STUDY.**

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BV associated with chemotherapy has been demonstrated to improve overall survival (OS) in metastatic CRC (mCRC). This allows to consider secondary resection of metastases and curative intent is presented here.

A total of 411 pts had 1st-line therapy with BV for mCRC: 347 were analyzable after 24 months of follow-up, and 67 (19.3%) had metastasis resection (pts operated, oPts).

- oPts main baseline characteristics were: mean age: 61.6 y, male: 46.3%, ECOG 0-1: 91.0% and one metastatic site: 58.2%; those of not operated pts (noPts) were: mean age: 64.9 y, male: 60.0%, ECOG 0-1: 75.7% and one metastatic site: 35.7%. Among the oPts, resection sites were: liver n=144, lung n=10, other n=20. Results of surgery available for 36 oPts were: R0-R1: 85.7%, R2: 14.3%.

- The median time from BV initiation to 1st resection was 207 days. For oPts, BV was mainly associated with irinotecan-based regimens (97.0%) and with FOLFOX regimens (3.0%); for noPts it was: FOLIFIRI: 83.6%, XELOX: 9.6%, FOLFOX: 7.0% and FOLFIRINOX: 0.4%.

- Objective response rate was 65.1% including 32.8% complete response (vs 49.3% and 5.4% for noPts), stable disease 14.9% (vs 30.6%) and absence of progressive disease (vs 17.1%).

- Median duration of BV treatment was 6.9 months and of 1st-line therapy was 14.3 months (vs 5.0 and 8.3 months for noPts). Median PFS was 13.6 months for oPts, the 1-yr OS rate was 94.0% (95%CI 84.9-97.7) and the 2-yr OS rate was 81.7% (95%CI 70.0-89.2) in oPts and was 21.9 months for noPts.

- For pts treated by BV in a real-life setting, secondary resection of mCRC for initially unresectable metastases was possible for 19% of pts with 85.7% R0-R1. Evaluation of morbidity and longer follow-up will allow the real long-term benefit to be studied.

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may be explained by higher DCR rates in the FU/IRI pts. Patients who underwent hepatic resection showed favorable long-term survival with median OS 43.8 months and 5-year-survival of 37.1%.

Disclosure: All authors have declared no conflicts of interest.

**L33P**

THE ROLE OF PERIOPERATIVE BEVACIZUMAB IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER AND LIVER METASTASES TREATED WITH LIVER METASTASECTOMY

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**Background:** Patients with colorectal cancer (CRC) and liver metastases benefit from perioperative chemotherapy (Ch) and liver resection. There is still concern among clinicians of the impact of adding Bevacizumab (B) on liver resection complications.

**Patients and methods:** This is a single centre retrospective analysis of outcomes of patients with CRC and liver metastases treated with perioperative Ch + B followed by liver resection. Seventy-seven patients, 46 males, 31 females, were identified from our prospectively maintained database.

**Results:** The majority of patients (74%) received Oxaliplatin based Ch. Nearly half of the patients (46%) received it in addition to Ch. Over 70% received systemic treatment pre and post liver resection with the remaining receiving perioperative treatment alone. The median time from neoadjuvant Ch + B to liver resection was 62 days (33-181) and the median time between liver resection and adjuvant chemotherapy was 62 days (18-115). The rate of B resections was 29/41 (70%) in the Ch and 22/36 (61%) in the Ch+B group (p<0.373, non significant). Postoperative complications developed in 25/41 (61%) patients who received Ch alone and 25/36 (69%) patients who received Ch+B (p=0.604, non significant). Complications observed in the Ch+B group included: liver dysfunction (predominantly hyperbilirubinaemia) (17/36=47%), cardiac abnormalities (6/36=16%), infection (5/36=14%), respiratory problems (4/36=11%), wound dehiscence (3/36=11%), DVT/PE (2/36=5%), bleeding/thrombosis (2/36=5%). No significant association was found between predictive factors (age, gender, performance status, previous metastases, number of liver metastases) and greater benefit with the addition of B in improving PFS or OS. No association was found between time from chemotherapy to surgery and complication rates.

**Conclusion:** The addition of B to standard chemotherapy does not increase liver resection complication rates. Larger studies are required to determine the impact of the addition of B on survival.

Disclosure: I. Chau: Advisory board and honorarium from Roche. D. Cunningham: Research funding and advisory board (unpaid) from Roche. All other authors have declared no conflicts of interest.

**L33P**

LIVER RESECTION PLUS LOCAL DESTRUCTION OF LIVER METASTASES FOR PATIENTS WITH METASTATIC COLORECTAL CANCER

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**Introduction:** Due to initial wide spread of the disease only 4-15% pts with colorectal liver metastases (CLM) receive radical liver resections and most pts receive only palliative chemotherapy. 5-year overall survival in this group of pts is less than 5%. The aim of our study was to increase overall survival of pts with CLM by the use of liver resection in combination with local destruction methods.

**Methods:** Retrospective analysis included 527 pts with CLM who had received surgical treatment in 1990-2008. Out of them 496 pts underwent liver resections (liver resection group) and 31 pts - simultaneous liver resections and local destructive methods (combined group) - radiofrequency ablation (11 pts) or cryoablation (20 pts). Indications for these procedures were localization of lesions near major blood vessels or bile ducts and cases when future remnant liver volume would be less than 25%. Twenty five pts received the following postoperative chemotherapy: FOLFOX (n=13), FU/LV (n=7) or other regimens (n=5). Postoperative complications of the combined group and the liver resection group were compared and overall survival rate in the combined group was calculated.

**Results:** Median overall survival in the group of liver resection combined with local destruction methods was 26 months, 5-year survival rate was 20.8%. The median blood-loss in the liver resection group was 1450 ml (50.0 – 10000.0 ml). Posturgical complications occurred in 158 pts (31.9%), 16 pts died (3.2%). Liver failure was the most common complication, developing in 83 pts (16.1%). Bile fistula was second-ranking complication (46 patients, 9.3%). The median blood-loss in the combined group was 1500 ml (400.0 – 4000.0 ml), mortality rate - 3.2% (1 patient), posturgical complications occurred in 8 cases (23.8%), liver failure – in 3 cases (9.7%) and bile fistula – in 3 cases (9.7%).

**Conclusion:** Combined treatment for CLM including liver resection and local destruction methods do not increase surgical complications and seem to increase overall survival rate in the group of pts with unresectable CLM. Disclosure: All authors have declared no conflicts of interest.

**L33P**

TREATMENT FOR RECURRENT AFTER HEPATECTOMY IN PATIENTS WITH COLORECTAL LIVER METASTASIS

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**Aims and patients:** This retrospective study was performed with data of 202 patients, who underwent hepatectomy for solitary or multiple liver metastasis from colorectal cancer, to evaluate factors influencing the long-term survival and therapeutic significance for recurrence after initial hepatectomy.

**Results:** Cumulative 5 and 10 year survival rates after initial hepatectomy were 44.1% and 31.4%, and cumulative 5 and 10 year disease-free survival were 18.5% and 18.3%, respectively. Survival rates were not significantly different among the patients with solitary liver metastasis, those with 2 or 3 metastases and those with 4 or more metastases. After diagnosis of recurrence in 153 patients, repeat resection was performed in 73, chemotherapy alone in 36, and best supportive care in 44. Between patients with solitary and plural liver metastases, overall survival rate was not different but the former had significantly better disease-free survival rate. Also, survival rates after recurrence were not significantly different between those two patients groups. These findings indicate that treatment after recurrence might improve survival in patients with plural liver metastases. In patients who underwent hepatectomy for solitary liver tumor at initial hepatectomy, those eligible for surgical resection for recurrent sites had significantly better survival rates than patients with best supportive care, but not different from patients with chemotherapy alone. In patients with plural metastatic liver tumors at initial hepatectomy, those eligible for surgical resection for recurrent sites had significantly better survival rates than patients with chemotherapy alone and than patients with best supportive care, suggesting that surgical resection provided survival benefit as a therapeutic approach on just patients with plural liver metastasis at initial hepatectomy than those with solitary liver tumor.

**Conclusions:** Although high recurrence is inevitable after resection of multiple liver metastases from colorectal cancer, surgical resection after recurrence could promise prognosis equal to solitary liver metastasis for patients with multiple liver metastases at initial hepatectomy.

Disclosure: All authors have declared no conflicts of interest.

**L40P**

A RANDOMIZED PHASE III TRIAL OF ADJUVANT CHEMOTHERAPY WITH IRINOTECAN, LEUCOVORIN AND FLUOROURACIL verses LEUCOVORIN AND FLUOROURACIL FOR STAGE II AND III COLON CANCER: A HELLENIC COOPERATIVE ONCOLOGY GROUP STUDY

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**Background:** Irinotecan (CPT-11), a topoisomerase I inhibitor, is effective when combined with 5-fluorouracil (5FU) and leucovorin (LV) for the treatment of metastatic colorectal cancer. When this study was designed 5FU plus LV was standard treatment for colon cancer. We evaluated the efficacy and safety of weekly bolus irinotecan plus 5FU plus LV in the treatment of patients with stage II or III colon cancer.

**Methods:** The study included 873 eligible patients. The treatment consisted of weekly administration of irinotecan 80 mg/m² intravenously (IV), LV 200 mg/m² and 5FU 450 mg/m² (Arm A) versus LV 200 mg/m² and 5FU 450 mg/m² bolus (Arm A) versus LV 200 mg/m² and 5FU 350 mg/m² bolus (Arm B). In Arm A treatments were administered weekly for 4 consecutive weeks, followed by a 2-week rest, for a total of six cycles, while in Arm B treatments were administered weekly for 6 consecutive weeks, followed by a 2-week rest, for a total of four cycles. The primary end point was disease-free survival (DFS) at 3 years.

**Results:** There were no differences between the arms in 5-year overall and disease-free survival. With the exception of leucopenia and neutropenia, which were higher in patients in Arm A, there were no significant differences in Grade 3 and 4 toxicities between the two regimens. The most frequently recorded Grade 3/4 toxicity was diarrhea in both treatment arms.

**Conclusions:** Irinotecan added to weekly bolus 5FU plus LV did not result in improvement in disease-free or overall survival in stage II or III colon cancer, but did increase toxicity.

Disclosure: All authors have declared no conflicts of interest.
Background: Adjuvant capecitabine is at least equivalent to bolus i.v. 5-FU/LV. NO16968 compared XELOX with bolus i.v. 5-FU/LV for stage III colon cancer. In a planned safety analysis, XELOX had an acceptable safety profile (Schmoll et al. 2007). In a recent analysis of the ACCENT database, investigators concluded that the improved efficacy associated with newer adjuvant regimens vs. 5-FU/LV may not be preserved in patients aged ≥70 years (McCleary et al. 2009).

Methods: Pts were randomized to either XELOX (capecitabine 1000mg/m² bid d1–d14 + oxaliplatin 130mg/m² iv d1, q3w x8) or bolus i.v. 5-FU/LV: Mayo Clinic (LV 200mg/m² + 5-FU 425mg/m² d1–5, q4w x6) or Roswell Park (LV 500mg/m² + 5-FU 500mg/m² d1, w1–6 in 8w cycles x4). Treatment effects of XELOX vs. 5-FU/LV were assessed by age (≥65y, planned; >70y, unplanned).

Results: Of the 1886 pts randomized, 1864 were evaluated in the previously reported safety analysis. After median follow-up of 57 months, 1886 pts (ITT) were evaluated for DFS (primary endpoint), which was significantly superior for XELOX (HR=0.88, 95% CI, 0.69–0.99, p=0.0064). Analysis of 3-y DFS and 5-y OS in pts >70y and ≥70y showed a similar advantage of XELOX over 5-FU/LV.

Conclusions: XELOX is superior to bolus 5-FU/LV for DFS as adjuvant treatment for stage III colon cancer; these findings confirm the benefits shown with oxaliplatin plus 5-FU combinations in stage III pts. Efficacy benefits are maintained for DFS and OS in pts ≥70y, in contrast to results from ACCENT and MOSAIC, in which no significant benefit was shown with the addition of oxaliplatin to 5-FU/LV in this age group. Reasons for this apparent difference are unknown. Current OS data indicate a trend towards superior survival with XELOX. XELOX is an effective adjuvant therapy and should be considered for all eligible patients.

Disclosure: D. Haller: Member on Advisory board: Roche, Sanofi-Aventis; Corporate-sponsored research with Roche Honoraria: Roche, Sanofi-Aventis

J. Cassidy: Member on Advisory board: Roche, Sanofi-Aventis; Corporate-sponsored research with Roche, Sanofi-Aventis Honoraria: Roche, Sanofi-Aventis

J. Taberner: Member on Advisory board: Roche, Sanofi-Aventis Honoraria: Roche, Sanofi-Aventis

J. A. Maroun: Member on Advisory board: Roche Corporate-sponsored research with Roche Honoraria: Roche

F. De Braud: Member on Advisory board: Sanofi-Aventis Honoraria: Sanofi-Aventis

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E. van Cutsem: Member of Advisory board for F. Hoffmann-La Roche Corporate-sponsored research from F. Hoffmann-La Roche

F. Gilberg: Own stock: Member of Roche Connect and owning Roche Genuscheine Employed by Roche

H. Schmoll: Member on Advisory board: Roche, Merck, Merck-Scharpe and Documentary-Corporate research with Roche, Merck Honoraria: Roche, Merck, Astra-Zeneca

All other authors have declared no conflicts of interest.
a high amount of stroma (stroma-high) and with less stroma (stroma-low). In total 135 stage II and III colorectal cancer patients were analyzed for markers involved in pathways related to stromal production and epithelial-mesenchymal transition (EMT). Treatment with a COX-2 inhibitor might improve patient outcome in those patients with a high percentage of stroma. A total of 146 patients treated either with placebo or COX-2 inhibitor was analyzed (VICTOR-trial).

Results: Of 136 analyzed patients 35 (25.7%) were stroma-high and 101 (74.3%) stroma-low. Significant differences in survival were observed, with stroma-high patients showing poor survival (OS p<0.001, HZ 2.29; DFS p=0.0002, HZ 2.31). A high-risk group was identified with stroma-high and SMAD4 loss (OS p=0.008, HZ 7.98, CI 4.12-15.44; DFS p=0.005, HZ 6.57, CI 3.43-12.56; 12 of 14 (85.7%) patients died within 3 years. In a logistic-regression analysis a high proportion of stroma and SMAD4 loss were strongly related (HZ 5.42, CI 2.13-13.82, p<0.001). Results of the COX-2 inhibitor are currently under evaluation but will be presented at the conference.

Conclusions: Conventional haematoxylin-eosin stained tumor slides contain more prognostic information than simply noting the amount of stroma. This can be unfeasible by assessing the tumor-stroma ratio. It should be considered to implement this parameter in standard pathological reports in addition to the TNN classification.

Disclosure: All authors have declared no conflicts of interest.

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IN MUCINOUS CARCINOMA AN INDEPENDENT HISTOLOGIC TYPE IN COLON CANCER? A SIGNIFICANCE OF MUCIN IN HISTOLOGIC CLASSIFICATION.

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The histologic classification of colon cancer (CC) has been decided on the basis of the predominant histological appearance. Cases in which mucin component occupied in more than 50% or 60% in cancer tissue are classified as mucinous adenocarcinoma. However, there is controversy as to whether there is any difference in biological activity or prognosis from adenocarcinoma, which accounts for the majority of CC. Previous studies have made comparisons between mucinous carcinoma and non-mucinous adenocarcinoma, and there have been no studies according to the proportions of mucin. In the present study we investigated the significance of the mucin area ratio in cancer tissue as a predictor for prognosis.

Methods: The subjects were 1039 patients with CC between 1991 and 2005, and we evaluated the mucin area ratio on the maximal cut surface of the pathological specimen. Associations between age, gender, histological type, mucin area ratio, Stage, tumor-stroma ratio, and survival were analyzed.

Results: Mean age was 64.5±12.2 years (median age: 65 years). Histologic grade was highly differentiated adenocarcinoma in 554 cases (53%), moderately differentiated adenocarcinoma in 434 cases (41%), and poorly differentiated adenocarcinoma in 26 cases (3%). A total of 103 cases (10%) were Stage I, 405 (39%) were Stage II, 312 (30%) were Stage III, and 217 (21%) were Stage IV.

Adjuvant chemotherapy mainly consisted of oral fluoropyrimidines was administered in 398 cases (56%). No mucin was present in 878 cases (84%). The mucin area ratio were Stage IV. Adjuvant chemotherapy mainly consisted of oral fluoropyrimidines was administered in 398 cases (56%). No mucin was present in 878 cases (84%). The mucin area ratio were more than 50% or 60% in cancer tissue are classified as mucinous carcinoma. However, there is controversy as to whether there is any difference in biological activity or prognosis from adenocarcinoma, which accounts for the majority of CC. Previous studies have made comparisons between mucinous carcinoma and non-mucinous adenocarcinoma, and there have been no studies according to the proportions of mucin. In the present study we investigated the significance of the mucin area ratio in cancer tissue as a predictor for prognosis.

Conclusions:

Results: Of 136 analyzed patients 35 (25.7%) were stroma-high and 101 (74.3%) stroma-low. Significant differences in survival were observed, with stroma-high patients showing poor survival (OS p<0.001, HZ 2.29; DFS p=0.0002, HZ 2.31). A high-risk group was identified with stroma-high and SMAD4 loss (OS p=0.008, HZ 7.98, CI 4.12-15.44; DFS p=0.005, HZ 6.57, CI 3.43-12.56; 12 of 14 (85.7%) patients died within 3 years. In a logistic-regression analysis a high proportion of stroma and SMAD4 loss were strongly related (HZ 5.42, CI 2.13-13.82, p<0.001). Results of the COX-2 inhibitor are currently under evaluation but will be presented at the conference.

Conclusions: Conventional haematoxylin-eosin stained tumor slides contain more prognostic information than simply noting the amount of stroma. This can be unfeasible by assessing the tumor-stroma ratio. It should be considered to implement this parameter in standard pathological reports in addition to the TNN classification.

Disclosure: All authors have declared no conflicts of interest.

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consisted of either 5-FU or oxaliplatin based regimens. Effects of age, sex, tumor (tm) localization, tm diameter, T stage, N stage, number of total lymph nodes (LN) dissected, TNM stage, lymphatic invasion (LI), vascular invasion (VI), PNI, presence of mucine and tm grade on DFS were assessed w univariate analysis. DFS was determined using the Kaplan-Meier method, w differences determined by multivariate analysis using the Cox multiple hazards model. Results were compared using the log-rank test.

Results: A total of 209 pts (99 female) w early stage CRC were analyzed retrospectively. The median follow-up was 29.1 months (1-27.1). The median age was 59 (range: 19-81). The rates of T2, T3, and T4 tms were 4%, 7%, and 17% respectively. 40% of the primary tms were localized at rectum, 28% at sigmoid and 19% at right colon. LI, VI and PNI rates were 9.7% 21% 33% respectively. 80% of pts received 5-FU based regimens. 3-yr DFS for all pts was 50%. Stage III pts had significantly more PNI (25% of Stg II pts, 56% of Stg III pts, p<0.000). Univariate analyses revealed rectal localization (p<0.001), T2 disease (p<0.000), TNM stage (p<0.001), VI (p=0.03), LI (p=0.013), PNI (p=0.05) and presence of mucine (p=0.033) as prognostic factors for DFS. In multivariate Cox regression analysis; rectal disease, vascular invasion and TNM stage were independent prognostic factors for DFS.

Conclusion: On the contrary to some published reports, in the multivariate model, this study is unable to show the preanalysys hypothesis of prognostic importance of PNI on DFS in curatively resected early stage CRC pts. However it still seems to need more homogenous groups w larger number of pts to clarify this issue.

Disclosure: All authors have declared no conflicts of interest.

PERINEURAL INVASION IS A STRONG INDEPENDENT PROGNOSTIC FACTOR FOLLOWING PRE-OPERATIVE CHEMO/RADIOThERAPY FOR LOCALLY ADVANCED RECTAL CANCER

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Aims: To assess the prognostic value of perineural invasion following pre-operative chemo/radiotherapy in patients with locally advanced rectal cancer.

Methodology: The study involved 94 patients with locally advanced rectal cancer treated with preoperative radiotherapy at Nottingham University Hospital between April 2001 and December 2005. Patients were treated with CT planned radiotherapy to a dose of 50Gy in 25 fractions over 5 weeks or without concurrent chemotherapy at a dose of 1650mg/m2/day. Surgery was performed after an interval of 6-10 weeks. The median follow-up was 40 months (range 3-90 months).

Results: Perineural invasion was found in 19 patients (20%) in keeping with recent literature. It was found to be a strong independent prognostic factor for both disease free (p<0.0001) and overall survival (p=0.002) on Kaplan-Meier analysis. Median DFS was 12 months and OS 30 months in patients with perineural invasion. Median DFS and OS were not reached at 3 years in patients without perineural invasion. On multivariate analysis perineural invasion, nodal status, tumour regression grade and circumferential resection margin status were the most powerful predictors of both disease free and overall survival.

Conclusions: Perineural invasion is a poorly reported but very strong prognostic factor and predicts for long term outcome following preoperative chemoradiotherapy in rectal cancer. It’s presence should be considered when making decisions about adjuvant treatment in rectal cancer.

Disclosure: All authors have declared no conflicts of interest.

EARLY DETECTION OF COLORECTAL CANCER USING MASS SPECTROMETRY BASED SERUM PROTEIN PROFILING

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Objective: Colorectal cancer (CRC) is among the most common malignancies and a leading cause of cancer-related morbidity and mortality. Early diagnosis is the most influential factor to reduce disease-related mortality. Currently only high-risk patients receive screening colonoscopy. Due to its invasive character, colonoscopy is not suitable for population-wide screening. A specific and more sensitive alternative to screening colonoscopy could be the use of proteomic biomarkers in serum.

Methods: In a randomized block design pre-operative serum samples obtained from 66 colon cancer patients and 50 controls were used to generate MALDI-TOF protein profiles using C8 magnetic beads. Next, for the analysis of a new patient series with improved magnetic beads (WCCX), serum samples were obtained from 200 CRC patients and 400 healthy controls. A calibration set and a validation set were composed. MALDI-TOF protein profiles were generated after automated fractionation and spotting (96-channel pipetting robot, Hamilton Robotics). The spectra generated using mass spectrometry (Ultraflex) were smoothed, binned and normalized after baseline correction. Linear discriminant analysis with double cross-validation, based on principal component analysis, was used to classify the protein profiles.

Results: The first study using 58 magnetic beads showed a sensitivity of 95% and a specificity of 90% in detecting CRC with an AUC of 97%. For the new series using WCCX magnetic beads preliminary results show similar results. Detailed examination for different tumor stages is under evaluation. Furthermore first results are becoming available for the evaluation of serum profiles as a prognosticator.

Conclusion: The results obtained in both studies indicate potential applicability that serum protein profiles can be an option for the early detection of CRC. The automated procedure shows robust results which can be further developed for use in a population-wide screening protocol.

Disclosure: All authors have declared no conflicts of interest.

DEVELOPMENT AND MEASUREMENT OF GUIDELINE-BASED INDICATORS FOR COLORECTAL CARCINOMA

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Background: Guideline adherence is not always optimal for patients with cancer. To provide information on guideline recommendations that need improvement for patients with colon and rectal cancer (CRC), this study aimed to develop and measure adherence to guideline-based indicators for CRC.

Methods: Indicators for CRC were systematically developed for diagnosis, treatment, follow-up and the organization of care using a two round RAND modified Delphi procedure. Potential guideline-based indicators were rated and then discussed in a face-to-face meeting on their usefulness to measure the quality of care. The final set was measured in a retrospective study in 22 hospitals from 3 regions in the Netherlands. Data on indicator adherence were collected by the Comprehensive Cancer Centres East, North-East and Limburg from medical records for 652 patients with CRC (diagnosed in 2006-2007). Indicators with scores < 90% were defined as having potential for improvement.

Results: Nineteen indicators were developed: seven for diagnosis, five for treatment, two for follow-up and five for the organization of care. Improvement potential was observed for 17 indicators. Lowest scores for diagnosis concerned the CT or MRI imaging of the liver (48%) and the preoperative assessment of circumferential margins (47%). Potential for improvement was observed for radio-chemotherapy for locally advanced rectal cancer (43%) and administration of bevacizumab in combination with chemotherapy for metastatic CRC (47%). For follow-up, a postoperative colonoscopy (in case preoperative image was incomplete) was performed in 32% of the patients with colon cancer and determination of serum carcino-embryonic antigen and performance of a CT-scan or ultrasound of liver within 6 months was performed in 15%. For the organization of care, only a minority of patients was discussed in a multidisciplinary team (32%).

Conclusion: In this study, nineteen indicators were developed for CRC of which the majority needed improvement. These results provide useful information to improve adherence to guideline recommendations and hence improve the quality of care for patients with CRC.

Disclosure: All authors have declared no conflicts of interest.

MMTG - ES05-T POLYMORPHISM IS ASSOCIATED WITH PROGNOSIS FOR PATIENTS WITH METASTATIC COLORECTAL CANCER TREATED WITH OXALIPLATIN-BASED CHEMOTHERAPY

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The present study analyzed the polymorphisms of DNA repair genes and their impact on the response to chemotherapy and survival of patients with colorectal cancer. A total of 94 patients with recurrent or metastatic colorectal cancer treated with oxaliplatin-based combination chemotherapy were enrolled in the present study. The single nucleotide polymorphisms of 16 DNA repair genes were determined using a PCR-RFLP assay. During the median follow-up duration of 15.9 (2.1 - 53.0) months, 67 (71.3%) progression and 29 (30.9%) deaths were observed. Among the 60 patients assessed for response, response to the oxaliplatin-based regimens was found in 27 (45%) patients (9 CR and 18 PR). In a logistic regression analysis adjusted to age, sex, primary site, disease status, and regimen, the POLR2C rs4957 and MSH2 rs1732183 polymorphisms were statistically associated with the response to the oxaliplatin-based
No correlation between the number of mRNA copies of genes coding IGF and BMI in tissues representing different clinical staging but the analysis showed the higher method.

Epidemiological researches indicate that obesity is the risk factor of colorectal cancer. The purpose of the study was to analyze mRNA expression profile of genes coding IGF in the colorectal cancer patients. The median age of the patients was 64 years (range, 21-85), and 251 (56.5%) patients had colon cancer and 193 (43.5%) patients rectal cancer. Pathologic stages were found. The analysis should be continued consideration body mass index for the same clinical staging. The findings suggest that the changes of expression profile of genes coding IGF could be connected with autocrine and paracrine function of tumor inhibition in colorectal cancer. This study was supported in part by a Ministry of Scientific Research Grant NN401467234.

Disclosure: All authors have declared no conflicts of interest.

IS OBESITY CHANGES THE EXPRESSION PROFILE OF GENES CODING IGF IN THE COLORECTAL CANCER PATIENTS?

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Epidemiological researches indicate that obesity is the risk factor of colorectal cancer. The fatty tissue is a place of synthesis and excretion of many cytokines as IGF1, TNFα, IL-6, VEGF, TGFβ, leptin, adiponectin and others. The aim of the study was to analyze mRNA expression profile of genes coding IGF in relation to body mass index (BMI) in the colorectal cancer patients.

Material and methods: The colon cancer specimens were taken during surgery treatment of 35 colorectal cancer patients (22 men; 13 women, aged 65 ± 8.9). Examined patients were divided into 4 groups according to BMI: stage I: 17 patients; stage II: 10 patients; stage III: 7 patients; stage IV: 1 patient. A number of mRNA copies of genes coding IGF, IGF2, IGFIR, IGF2R were examined with RT-PCR method.

Results: There were no statistical differences of mRNA copies of genes coding IGF, IGFIR, IGF2, IGF2R in the tumor tissue between examined groups A and B. But the analysis showed that the number of mRNA IGF1 was higher in the patients with overweight and obesity than in the group with normal weight (1505 ± 240 vs. 858 ± 249). The level of mRNA genes coding IGF were similar in tissues representing different clinical staging but the analysis showed the higher number copies of IGF1, IGF1R, IGF2R according to advancement of cancer. There were no correlation between the number of mRNA copies of genes coding IGF and BMI in the group A. But there was negative correlation between the number of IGF1 and BMI (R=−0.44 ± 0.30) and positive correlation between the number of IGF2R and BMI (R=0.54 ± 0.03) in the group B.

Conclusion: The changes of expression profile of genes IGF and its receptors in colorectal cancer patients according to body mass were found. The analysis should be done among patients according to level of advancement of colorectal cancer, taking into consideration body mass index for the same clinical staging. Further studies are warranted to clarify the role of IGF genes polymorphisms as biomarker for colorectal cancer.

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Weeks after completion of CRT. Tumor regression grades (TRG) were evaluated on surgical specimens according to Dworak. The primary endpoint was complete pathological response (pCR).

**Results:** Forty-two of 61 pts enrolled were eligible for safety and efficacy analyses. Median stage was 60 (range: 31–79) years, 64% of pts were male. Seven pts (16.6%) had T3N0 tumors, 11 pt (26.3%) T1N1, 2 pt (4.7%) T2N2, 18 pts (42.9%) T3N2, and 4 pts (9.9%) T4N2. In 22 pts (52.4%) tumor invaded the mesorectal fascia. The median tumor distance from anal verge was 6 (range 0–11) cm. All pts received 30.4 Gy RT and 4 Bev infusions. Temporary capcitabine intake interruption was necessary for 2 pts (4.8%) due to leucopenia grade 2, for 1 pt (2.4%) due to leucopenia grade 3 and for 1 pt (2.4%) due to diarrhea grade 3. Other grade 3 toxicities included dermatitis (n=6, 14.3%) and proteinuria (n=3, 7.1%). Radical resection was achieved in 39 pts (92.9%) and 31 pts (73.8%) had sphincter preserving surgery. TRG 4 (pCR) was recorded in 5 pts (11.9%) and TRG 3 in 6 pts (14.3%). -T-, N- and overall downstaging rates were 45.2%, 73.8% and 73.8%, respectively.

**Conclusions:** This updated analysis shows the feasibility of preoperative CRT with bevacizumab and capcitabine. The observed adverse effects of neoadjuvant treatment in our study are comparable to those previously reported, but the pCR rate appeared to be much lower.

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** The treatment of locally advanced rectal cancer with preoperative radiotherapy and concurrent 5-fluorouracil (5-FU)-based chemotherapy on improves local tumor control, increasing resectability and rate of sphincter preservation.

**Aim:** Comparing the results of preoperative chemoradiotherapy with continuous infusion of 5-FU versus capcitabine (C) in the treatment of locally advanced rectal cancer in our institution.

**Material and methods:** Retrospective analysis of clinical records of patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy between January 2003 and January 2010 in our institution. Chi-square test was used to establish the relation between variables.

**Results:** There were 133 patients (39.8% female and 60.2% male), with a median age of 63-year-old at diagnosis. The primary tumor location was in lower rectum in 52.6% of patients, in medium rectum in 38.3% and in high rectum in 9.0%. The majority (62.4%) of patients presented with IBB clinical stage at diagnosis (stage IIA – 28.9%; IIB – 5.3%; IIBC – 0.8%; IVA – 2.9%). 5-FU was administered at a dose of 225mg/m2/day in continuous infusion during radiotherapy in 59.4% of patients, and C was given at a dose of 825mg/m2 twice a day in 33.1%. Patients received a total radiation dose between 46 and 50Gy, in 23 to 25 fractions, with 18MV energy. All patients underwent definitive surgery 6-8 weeks after chemoradiotherapy completion. Low anterior resection was made in 50.4% of patients and abdominoperineal resection in 39.8%. In 31.1% of patients with lower rectum tumors, sphincter preservation was made possible.

Downstaging was achieved in 60.9% of cases and a pathological complete response (pCR) was observed in 7(19%) and central review changed 5(13%) patients who had surgery. 5(13%) had Gr 3/4 pain, fatigue or infection. Pre-specified pre-op toxicities were diarrhea 10(24%), pain 4(9.5%) and fatigue 4(9.5%). Of 38 patients who had surgery 3(19%) had Gr 3/4 pain, fatigue or infection. Pre-specified AEs are presented in Table I. pCR was seen in 7(19%) and central review changed pathological stage in 6(16%) of cases.

**Conclusions:** In this study, Bev added to Ox and Cap in combination with radiation was safe but did not significantly increase pCR. Further study of pre-operative Bev with other regimen or induction chemotherapy may be warranted. Central pathology review should be considered for trials with pCR as the primary endpoint.

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In this study in order to demonstrate the relevance of the timing of bevacizumab (BEV) added to primary chemotherapy (CT) and radiotherapy (RT) we evaluate two different schedules of BEV in pts with locally advanced rectal cancer. Changes of circulating endothelial cells (CECs) and glucose metabolism, evaluated by flow cytometry and FDG-PET respectively, were used as early surrogate markers of tumor response. Thirty-two patients (inclusion criteria: cT4a, cT4b, cN0, T2s 5 cm from the anal verge and/or TVE CRM, M1 resectable/initiately unresectable) received 3 biweekly courses of oxaliplatin (100mg/m2) radiated (2.5mg/m2) on day 1, and fluorouracil (800mg/m2) folinic acid (250mg/m2) on day 1 during pelvic RT (45 Gy). In schedule A (16 pts) BEV (5mg/kg) was given biweekly from day 14 to 4 courses, while in schedule B (16 pts) it was given from day 4 for 2 courses. According to the Simon’s two-stage design, assuming a hypothesis of a 50% TRG1 (α=error=0.05, β=error=0.20), at least 6/16 TRG1 should be obtained (first stage) to continue pts. Grade 4 neuropenia was the most common adverse event with the schedule A (7 pts, 44%), but it was considerably lower with the schedule B (2 pts, 13%). Notably, a significant difference of CEC levels, compared to basal levels, was observed, 2 days after first cycle of CT, between the two schedules of treatment (median -66% vs -84% in schedule A and B, respectively, P<0.05). Likewise, a major reduction of median tumor metabolic volume was observed. 12 days after first cycle of CT, in schedule B compared to schedule A (75% vs -50%, P<0.05). Furthermore, while in the schedule A only 2 (12%) pts obtained a TRG 1 in the schedule B the number of TRG 1 required by statistical design was reached in the first 16 treated pts (96%). Therefore, accrual in the schedule B will continue to complete the second stage. Overall these data suggest the relevance of the BEV schedule to optimize the feasibility and efficacy of combination treatment, as well as the potential role of CEC evaluation and...
Background: Lymphangiogenesis and angiogenesis are essential for tumor development and progression. The lymphatic vessel density (LVD) and blood vessel density (BVD) and their relationship to outcome have been studied extensively, however the clinical significance of the location of LVD/BVD in tumor is not known. In the present study, the location and degree of LVD/BVD and their relationship to preoperative radiotherapy (RT), clinicopathologic, histopathologic and biologic factors were studied in rectal cancer patients participating in a Swedish clinical trial of preoperative RT.

Patients and methods: The location and degree of LVD/BVD were analysed in primary tumors (n=138/140) and their subgroups of non-RT (n=74) and RT (n=64/66). Further the degree of LVD/BVD was examined in the corresponding distant normal mucosa (n=35/31) and adjacent normal mucosa (n=27/21). All sections were immunohistochemically examined by using D2-40 and CD34 antibodies.

Results: In the whole series of the patients, a higher LVD at the periphery was related to negative p53 expression (P=0.03) and favourable survival independent of TNM stage, differentiation and p33 expression (P=0.03). LVD was increased in p53 negative tumors after RT (P=0.01).

Conclusions: LVD at the periphery of the tumour was an independent prognostic factor in rectal cancer patients.

Disclosure: The author has declared no conflicts of interest.

Background: Results of our phase II trial in pts with LARC treated with standard radiation plus cetuximab, oxaliplatin and cetuximab have shown that this regimen is feasible without a significant improvement of pathohistological response (Rödel et al., 2008). Although a certain subgroup of pts might benefit, there is no effective method to predict treatment efficacy. To identify potential biomarkers, we analyzed EGFR, PTEN, Ki67, survivin and p53 by IHC to find predictors for tumor regression grading, PFS and OS.

Methods: Pre- and posttherapeutic specimens from 47 pts of the phase II trial were taken before treatment as biopsies and at the time of surgery. Correlation of expression pattern of the biomarkers was done with pathohistologic response (modified classification by Dworak et al., 1997), PFS and OS.

Results: EGFR expression was significantly lower (p<0.001) after treatment, with the proportion of pts with EGFR null-expression increasing from pretreatment 52% to posttreatment 91% (p=0.0002). Initial EGFR expression did not significantly correlate with response (p=0.12) nor with PFS or OS (p=0.59 and p=0.63). In contrast to EGFR, PTEN expression increased after treatment (p=0.004). Initial PTEN expression did not significantly correlate with response (p=0.36) and PTEN upregulation was neither associated with PFS nor with OS (p=0.99 and p=0.55). Posttreatment Ki67 expression was significantly lower (p=0.001) with a significant correlation between initial expression of Ki67 and response (p=0.06), PFS (p=0.11) or OS (p=0.31). We did not observe a significant association between pre- and posttreatment expression of survivin (p=0.09) and p53 (p=0.52) and regression grade. High initial expression of p53 was not found to be predictive for PFS (p=0.48) or OS (p=0.38) and survivin not significantly associated with PFS (p=0.58) or OS (p=0.68).

Conclusions: Cetuximab-based chemoradiotherapy resulted in downregulation of EGFR and Ki67 expression and in upregulation of PTEN. However, expression of EGFR, PTEN, Ki67, survivin and p53 did not predict tumor regression grading, PFS or OS.

Disclosure: A. Hartmann: Honoraria, C. Roedel: Honoraria, Research Funding; D. Arnold: Honoraria, Research Funding. All other authors have declared no conflicts of interest.
Results: The follow up period was 72 (0-95) months. A trend toward statistically significant worse survival was observed for the patient group 1 (38%) comparing to group 2 (57.6%) and group 3 (51.0%), but result was not statistically significant (30% vs 35%, p = 0.114). Topo IIα expression was not found to be statistically different among patients arranged according to the Dukes tumor stage (Dukes A = 35%; B = 35%; C = 52.5%; tumor stage with distant metastases = 40%). Also, there was no significant correlation between the topo IIα expression and tumor grade (G1 = 40%; G2 = 35%; G3 = 35%), vascular invasion (without = 35%, with = 40%) and lymph node affection (N0 = 35%, N+ = 40%).

Conclusion: No significant correlation between the mentioned clinicopathologic parameters and the topo IIα was identified. The only exception were the patients’ survival data which showed worse survival in patients with lower expression of topo IIα, but without statistical significance. Due to relative rarity of this type of research, additional studied in larger cohort of patient are needed.

Disclosure: All authors have declared no conflicts of interest.

A LET-7 MICRONOMA COMPLEMENTARY SITE POLYMORPHISM IN THE KRAS 3'-UTR REGION AS A GENETIC REGULATOR IN ADVANCED COLORECTAL CANCER

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Background: Although KRAS status has been identified as a strong predictor of outcome. The fact that the functional KRAS-LCS6 variant affects the KRAS expression led us to hypothesize a possible association between the KRAS-LCS6 polymorphism and skin toxicity were independently related with response (p<0.05). Seventy seven patients presented LCS6 T/T genotype (85%) while 14 were T/G and 3 were G/G alleles. The difference was statistically significant (p=0.002). While the mean father age at birth was 31.1 ± 7.3 in patients, it was 29.8 ± 8.4 in the controls. The difference was statistically significant too (p<0.003). It was detected that cancers other than colorectal is more frequent in first degree relatives of colorectal cancer patients (p<0.001). People smoking or quitting smoking have more risk for colorectal cancer (p=0.013). In this study we detected that children may have higher risk if mother and father are more than 30, at birth (p=0.002 and p=0.002, respectively). While the mean maternal age at birth was 27.2 ± 6.5 in patients, it was 26.4 ± 7.3 in the controls. The difference was statistically significant (p<0.002). While the mean father age at birth was 31.1 ± 7.3 in patients, it was 29.8 ± 8.4 in the controls. The difference was statistically significant too (p<0.003).

Results: In this study, it was determined that children may have higher risk if mother and father are more than 30, at birth (p=0.002 and p=0.002, respectively). While the mean maternal age at birth was 27.2 ± 6.5 in patients, it was 26.4 ± 7.3 in the controls. The difference was statistically significant (p<0.002). While the mean father age at birth was 31.1 ± 7.3 in patients, it was 29.8 ± 8.4 in the controls. The difference was statistically significant too (p<0.003).

Conclusion: Our data supports that some prenatal factors such as high paternal age at birth may be risk factors for colorectal cancers. So, more comprehensive studies are needed about the effects of prenatal factors.

Disclosure: All authors have declared no conflicts of interest.

PROGNOSTIC VALUE OF SERUM CARCINOEMBRYONIC ANTIEN (CEA) IN FIRST LINE TREATMENT OF ADVANCED COLORECTAL CANCER (ACRC)

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Background: The clinical value of CEA as the marker for monitoring the response of advanced colorectal cancer (ACRC) to systemic therapy is not clearly established. The aim of this study was to prospectively evaluate the usefulness of CEA.

Patients and methods: Previously untreated haematologically confirmed ACRC, age > 18 years and Karnofsky (PSK) > 60% were treated with capcitabine (850 mg/m2 twice a day p.o. on days 1-14), irinotecan (240mg/m2/day on day 1) and bevacizumab (7.5 mg/kg on day 1), in a 3-week cycle. Response was evaluated every 2-3 month. CEA was checked on day 1 of every cycle. Response by CEA was defined as a reduction of 50%, and progression as an increase of 30%.

Results: From March 2005 to July 2009, 148 patients entered in the study. All patients have progressed as first line treatment and 71 have died. CEA was no upper normal limit (ULN) in 106 (71.6%), 3x ULN in 84 (56.7%), inferior to 2x ULN in 13 (8.7%), and
normal (<5 ng/mL) in 29 (19.5%) pts. 15 pts with normal baseline CEA have progressed, and CEA increased in 8 (53%) during first or successive lines. For response, there were 62 pts truly positive (TP), 21 truly negative (TN), 24 false positive (FP), and 6 false negative (FN). So resulted in sensitivity (S) of 97% (CI 95%, 88.68-99.48%), specificity (Sp) of 46.67% (CI 95%, 31.93-61.96%), positive predictive value (PPV) of 73.03%, and negative predictive value (NPV) of 91.3%. An accuracy of 76.79%. For progression, there were 98 TP, 7 TN, 22 FN, and no FP. So resulted in S of 81.6% (CI 95%, 73.3-87.9%), Sp of 100% (CI 95%, 96.1-100%), PPV of 100%, and NPV of 24.1%. An accuracy of 75.6%. CEA indicated progression and response with a median of 46 and 43 days prior to the computed tomography (CT) scan, respectively. OS and TTP was statistically higher for patients with baseline CEA < 2 X Upper Normal Limit (UNL) and < 5 X UNL. TTP to first line treatment was higher if a response in CEA was detected (p= 0.001). Patients with no radiologic response but CEA response, a trend in TTP was detected (p=0.069).

Conclusions: CEA is simple and accessible test that can predict the radiologic behavior; and is a prognostic factor for OS or TTP. These results suggest that CEA could help in the decision of accelerate or delay CT scan in order to avoid un-useful treatments/CT scan.

Disclosure: All authors have declared no conflicts of interest.
THE ROLE OF CONTRAST-ENHANCED ULTRASOUND IN DETECTION OF LIVER METASTASIS FROM COLORECTAL CANCER: 2 YEARS UPDATE RESULTS

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Background: Up to 15-25% of patients with colorectal cancer (CRC) will develop metastatic liver metastases during the follow-up. The management and prognosis of these patients depend heavily on the early detection of metastases. The most effective surveillance strategy has not yet been established. The introduction of second generation ultrasound contrast agents have improved the ability of contrast-enhanced ultrasound (CEUS) in detecting and characterizing liver lesions, showing that its accuracy is comparable to that of spiral CT e MRI with a liver contrast agent, with a cost and a time saving. We are conducting a feasibility study in order to verify the sensitivity and specificity of CEUS in detecting liver metastases compared with the standard imaging modalities used in the follow up of CRC.

Methods: A prospective pilot study considering all patients with a diagnosis of CRC in high risk stage II, stage III or with a previous metastasectomy of the liver. In order to detect possible metastases, the patients were followed with a follow-up schedule including a six-monthly ultrasonography alternated to an annual CT and a six-monthly CEUS with SonoVue contrast agent for the first 3 years.

Results: The accrual was reached with 85 patients enrolled in 2 years. The percentage of liver progression detected was 18% so far we executed 190 CEUS, identifying 39 suspected liver lesions. The concordance between CEUS and CT/CE was 89% with 35/39 confirmed focal lesions. The percentage of false positive was 7% with 3/39 benign lesions. The percentage of false negative was less than 4% with 2/39 lesions resulted positive with additional MRI or CT. CEUS improve specificity and sensitivity compared with baseline ultrasonography. We had an histological confirmation in all cases except one.

Conclusions: Our results are strongly supporting the similar diagnostic performance and confidence of CEUS compared to these imaging modalities in the follow-up of CRC. According to the results of this study we are planning a validation protocol for CEUS as standard technique for liver metastases diagnosis.

Disclosure: All authors have declared no conflicts of interest.

OXALIPLATIN STOP-AND-GO STRATEGY WITH ORAL S-1 MAINTENANCE THERAPY IN ADVANCED COLORECTAL CANCER: CCGO-0704 STUDY

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Purpose: In metastatic colorectal cancer (mCRC), a combination of 5-fluorouracil and fluorouracil with oxaliplatin (FOLFOX) is one of the standard first-line regimen. The cumulative neurotoxicity of oxaliplatin often requires therapy to be stopped in patients who are still responding. The aim of this study was to evaluate modified FOLFOX6 (mFOLFOX6) with the intermittent oxaliplatin treatment and maintenance therapy with S-1, oral fluoropyrimidine derivative, in the first-line treatment of mCRC.

Patients and methods: Thirty patients with untreated mCRC were treated with six cycles of mFOLFOX6 (oxalitrex 85 mg/m², leucovorin 200 mg/m², 5-fluorouracil bolus 400 mg/m² and 5-fluorouracil continuous 2400 mg/m², every 2 weeks) followed by maintenance therapy with oral S-1 (1-80-102mg/body days 1-8, every 6 weeks). Reintroduction of mFOLFOX6 was scheduled after four cycles of S-1 or tumor progression. The primary study end point was duration of disease control (DCC).

Results: Twenty of the 30 patients (66.7%) who achieved responses or stabilizations received S-1 maintenance therapy. mFOLFOX6 was reintroduced in twelve patients (40.0%). Median DCC was 13.1 months. Median progression-free survival (PFS) was 9.0 months. Overall response rates and disease control rates were 40.0% and 80.0% for the initial mFOLFOX6, 15% and 45% for S-1 maintenance therapy and 25.0% and 58.3% for mFOLFOX6 reintroduction. Twenty-eight patients (93.3%) had peripheral neurophytosis during treatment, but grade 3 neurotoxicity was observed in only 1 patient (3.3%).

Conclusion: The planned oxaliplatin stop-and-go strategy with oral S-1 maintenance therapy was feasible first-line treatment for Japanese mCRC patients. Further prospective randomized control study is warranted.

Disclosure: All authors have declared no conflicts of interest.

A MULTICENTER FEASIBILITY STUDY WITH S-1, OXALIPLATIN AND ORAL LEUCOVORIN (SOL) FOR THE PATIENTS WITH UNTREATED METASTATIC COLORECTAL CANCER: THE RESULT OF INTERIM ANALYSIS

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Background: Previous phase I study with S-1, oxaliplatin and oral leucovorin (SOL) demonstrated well tolerability and efficacy in Japanese patients with metastatic colorectal cancer. The present feasibility study was conducted to confirm the safety and efficacy of SOL in Chinese patients with untreated metastatic colorectal cancer preliminary.

Methods: Eligibility: untreated, recurrent or unresectable advanced colorectal adenocarcinoma, age ≥20, ECOG Performance Status (PS) of 0-2, adequate organ functions, and no prior history of chemotherapy. The treatment schedule comprised S-1 (40-60mg) and LV 25mg bid for one week and 2 hour drip infusion of oxaliplatin (L-OHP) 85mg/m² on day 1, every repeated every 2 weeks.

Results: A total of 20 (median age: 65; range: 30-78) were enrolled between August 2009 and December 2009. There were 14 patients with colon cancer and 6 with rectal cancer. Of the 20 patients, 10 were initially diagnosed with metastatic cancer and 10 were relapsed cancer after surgery. Data cut-off date was March 15, 2010. In total, 115 cycles were administered (median 6 per patient; range 1-10). Toxicities and responses were evaluated in 20 patients. The common hematologic toxicities were neutropenia (55%), thrombocytopenia (45%) and anemia (25%). The common non-hematologic toxicities were fatigue (45%), diarrhea (35%), nausea/vomiting (30%) peripheral neurotoxicity (25%). The incidence of any adverse events (grade ≥3) was 40% (8/20), including diarrhea (20%), thrombocytopenia (10%) and nausea/vomiting (10%). Dose-adjusted was executed in 11 patients owing to AEs, including S-1 in 9 cases and L-OHP in 9 cases. Death due to adverse event was not observed. In 20 patients with measurable disease, the overall response rate was 45% (1 CR and 8 PR: 95% CI 23-68%) and the disease control rate was 90%(95% CI 68%-99%). Pathologic complete response was observed in 1 patient after 5 cycles of treatment. Median PFS was not reached.

Conclusions: This preliminary result indicates that the SOL regimen is well tolerated and effective in Chinese patients with metastatic colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.
BACKGROUND: Endoscopic appearance was evaluated using 4 categories (0-3) at baseline and on pathologic regression of the resected specimens. The endoscopic appearance was evaluated using 4 categories according to the Japanese criteria (0, 1a, 1b, and 2). A response based on the pathology was defined as a category of 2+ or greater. The pathologic regression was evaluated using 5 categories according to the Japanese criteria (0, 1a, 1b, 2, and 3). A response based on the pathology was defined as a category of 2+ or greater. The mRNA expression levels of pyrimidine-related enzymes and folate-related enzymes were marginally evaluated using a RT-PCR assay. The evaluation of predictive factors was based on differences in the mRNA expression levels between responders and non-responders.

RESULTS: Tumor responses based on endoscopic appearance and the pathologic regression were observed in 50% (10/20) and 25% (5/20), respectively. The respective median FPGS/TS ratios were 2.23 and 1.38 for responders and non-responders, respectively. The mRNA expressions of pyrimidine-related enzymes and folate-related enzymes were marginally evaluated using a RT-PCR assay. The evaluation of predictive factors was based on differences in the mRNA expression levels between responders and non-responders.

CONCLUSION: The combination of FPGS and TS mRNA expression levels in primary tumors may be useful for predicting the efficacy of oral UFT/LV treatment in patients with colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

RELATIONSHIP BETWEEN MRNA EXPRESSION LEVELS AND CLINICAL EFFICACY OF ORAL URACIL AND TEGAFUR/LEUCOVORIN CHEMOTHERAPY IN PATIENTS WITH COLORECTAL CANCER


Background: 5-Flourouracil (5-FU)/leucovorin (LV) and oral uracil and tegafur (UFT)/LV are widely used as standard adjuvant chemotherapy for colorectal cancer (CRC). We previously reported that poly(ADP-ribose) synthetase (PAPS) and g-glutamyl hydrolase (GGH) were associated with the reduced folate levels in CRC tissues after LV administration. In the present study, we examined the relationship between mRNA expression of pyrimidine and folate metabolism-related enzymes in CRC tissues and the efficacy of UFT/LV treatment.

Material and methods: Twenty CRC patients without prior treatment who were scheduled to undergo surgery were enrolled. They received oral UFT/LV for 2 weeks until 2 days before surgery. We evaluated the tumor response based on the endoscopic appearance and on pathologic regression of the resected specimens. The endoscopic appearance was evaluated using 4 categories (0-3). A response based on the endoscopic appearance was defined as a category of 2+ or greater. The pathologic regression was evaluated using 5 categories according to the Japanese criteria (0, 1a, 1b, 2, and 3). A response based on the pathology was defined as a category of 2+ or greater. The mRNA expression levels of pyrimidine-related enzymes and folate-related enzymes were marginally evaluated using a RT-PCR assay. The evaluation of predictive factors was based on differences in the mRNA expression levels between responders and non-responders.

Results: Tumor responses based on endoscopic appearance and the pathologic regression were observed in 50% (10/20) and 25% (5/20), respectively. The respective median FPGS mRNA expression values were 0.97 and 0.70 for responders and non-responders based on the endoscopic appearance. This difference was marginally significant (P = 0.070). No differences were observed between the other mRNA expression levels and the response were observed. However, when combined with thymidilate synthase (TS), the respective median FPGS/TS ratios were 2.23 and 1.38 for responders and non-responders, respectively. This difference was significant (P = 0.033).

Conclusion: The combination of FPGS and TS mRNA expression levels in primary tumors may be useful for predicting the efficacy of oral UFT/LV treatment in patients with colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

CORRELATION OF BRAF STATUS WITH CLINICAL RESPONSE TO CETUXIMAB IN KRAS WILD TYPE (KRAS WT) METASTATIC COLORECTAL CANCER (MCRC) PATIENTS - SINGLE INSTITUTION EXPERIENCE

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Background: KRAS mutation status in codon 12 and 13 is recognized as a predictive factor for resistance to anti-EGFR monoclonal antibodies. Other mechanism of resistance could involve activating mutations of the other main EGFR effector pathway. In recent clinical studies, it was published that BRAF wild-type (wt) is required for response and that the patients (pts) with BRAF mutation had significantly shorter PFS and OS than BRAF wt pts. We retrospectively analyzed BRAF status in KRAS wt pts. Patients treated with chemotherapy (ChT) in combination with cetuximab (cChT) were included in this study. cChT (Group B; N:9). The response to the treatment was evaluated by pathological response and the ChT-induced hepatic injury after resection of LCM in patients treated with neoadjuvant ChT with or without bevacizumab (BV).

Methods: Forty consecutive patients were evaluated retrospectively. We compared the pathological response in patients treated with ChT plus BV (Group A; N:14) or without cChT (Group B; N:9). The response to the treatment was evaluated by pathological analysis of tumour viability (Grade 1: no residual tumour; Grade 2: minimal residual tumour; Grade 3: moderate response; Grade 4: no definitive response identified). Liver injury was investigated, scored between 0 and 3 and compared with control-group of patients operated without neoadjuvant treatment (Group C; N:17).

Results: Groups were comparable for gender, pT, pN and primary tumour location (colon vs rectum). Patients from groups A-B were younger (59.8 vs 57.7 vs 68.7 years; p=0.002), had a higher rate of synchronous metastases and a higher number of metastases than patients from Group C. Patients treated with ChT + BV had higher rates of good histological response (Grades 1-2) than patients treated with ChT alone (78% vs 44%; p=0.034). Patients with a good histological regression had a non-significant benefit in overall survival over patients with a poor response (33.3 vs 26.8 months; p=0.328). No significant difference was found in the three groups with respect to sinusoidal dilation (p=0.78) or steatosis (p=0.067).

Conclusion: The addition of BV to ChT prior to resection of LCM provides a better histological regression rate compared with ChT alone. Good responder patients had a tendency to benefit in overall survival. In our series, no significant ChT-induced hepatic injury was found.

Disclosure: All authors have declared no conflicts of interest.

BEVACIZUMAB IMPROVES PATHOLOGIC RESPONSE IN PATIENTS TREATED WITH OXALIPLATIN-BASED CHEMOTHERAPY FOR COLORECTAL LIVER METASTASES: REPORT FROM A RETROSPECTIVE STUDY

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AIM: Histological response of liver colorectal metastases (LCM) to ChT may be graded and be associated with survival. The purpose of the study was to evaluate the pathological response and the ChT-induced hepatic injury after resection of LCM in patients treated with neoadjuvant ChT with or without bevacizumab (BV).

Methods: Forty consecutive patients were evaluated retrospectively. We compared the histological response in patients treated with ChT plus BV (Group A; N:14) or without ChT (Group B; N:9). The response to the treatment was evaluated by pathological analysis of tumour viability (Grade 1: no residual tumour; Grade 2: minimal residual tumour; Grade 3: moderate response; Grade 4: no definitive response identified). Liver injury was investigated, scored between 0 and 3 and compared with control-group of patients operated without neoadjuvant treatment (Group C; N:17).

Results: Groups were comparable for gender, pT, pN and primary tumour location (colon vs rectum). Patients from groups A-B were younger (59.8 vs 57.7 vs 68.7 years; p=0.002), had a higher rate of synchronous metastases and a higher number of metastases than patients from Group C. Patients treated with ChT + BV had higher rates of good histological response (Grades 1-2) than patients treated with ChT alone (78% vs 44%; p=0.034). Patients with a good histological regression had a non-significant benefit in overall survival over patients with a poor response (33.3 vs 26.8 months; p=0.328). No significant difference was found in the three groups with respect to sinusoidal dilation (p=0.78) or steatosis (p=0.067).

Conclusion: The addition of BV to ChT prior to resection of LCM provides a better histological regression rate compared with ChT alone. Good responder patients had a tendency to benefit in overall survival. In our series, no significant ChT-induced hepatic injury was found.

Disclosure: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.
BEVACIZUMAB IN COMBINATION WITH CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER: THE MCGILL EXPERIENCE

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Disclosure: All authors have declared no conflicts of interest.

Background: Bevacizumab (BV) prolongs overall survival (OS) and progression-free survival (PFS) when added to standard chemotherapy (CT) for metastatic colorectal cancer (mCRC). After approval of BV in Canada in 2005, this observational cohort study was designed to include patients (pts) receiving various CT regimens with BV in order to evaluate its safety and efficacy.

Methods: Eligibility criteria were minimized to facilitate enrolment of a typical mCRC population. Choice of the CT regimen was at physicians’ discretion. Predetermined endpoints were treatment characteristics, PFS, OS stratified by line of therapy that BV was initiated, and grade 3–4 adverse events (AE) likely related to BV. Pts were followed for up to 4 years, and clinical data updated every 3 months.

Results: 196 evaluable pts were enrolled at a single centre from April 2005 to Dec 2007. Median age: 55 (range 18–79), age 70–79: 12%; male 55%; ECOG PS 0/1: 12/27% 5/0%. First line CT choice (49% of pts) was oxaliplatin-based 55%, irinotecan-based 43%, or both oxaliplatin-irinotecan 2%. Second line CT choice (22% of pts) was oxaliplatin-based 39%, irinotecan-based 60%, or combined oxaliplatin-irinotecan 1%. Third or greater line CT choice (25%) of pts was oxaliplatin-based 25%, irinotecan-based 65%, or combined oxaliplatin-irinotecan 6%. In total, 47 AE were reported: thrombocytopenia in 8.6% of pts, venous thromboembolism 4.6%, hypertension 1.5%, bleeding 1.5%, bowel perforation 1.0%, nephrotic syndrome 0.5% posterior reversible encephalopathy syndrome 0.5%, and allergic reaction 0.5%. First line median PFS=10months (m), median OS=52m. Second line median PFS=6.5m, median OS=60m. Third line or greater median PFS=5.5m, median OS=58m.

Conclusions: The safety profile of BV in this population of mCRC pts with different third line or greater median PFS=5.5m, median OS=58m.

BEVACIZUMAB PLUS OXALIPLATIN-BASED CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER: AN INTERIM ANALYSIS OF 81 PATIENTS IN OUR INSTITUTION

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Disclosure: Neoadjuvant chemotherapy is standard of care for metastatic colorectal cancer. Bevacizumab prolongs progression-free survival (PFS) and median survival when added to chemotherapy for first-line treatment of patients with metastatic colorectal disease.

Methods: We retrospectively analysed 81 patients with metastatic colorectal cancer who were treated in our institution from 2005 to 2007. In October 2009. The aim of this study was to access progression-free survival and evaluate toxicity of therapy. There were 49 male and 32 female patients. As first line of chemotherapy for metastatic disease 37 patients received FOFLIRI in standard doses (Group I) and 44 FOFLIRI + bevacizumab 5mg / kg (Group II).

Results: Average number of applied cycles was for FOFLIRI 9.4 ± 4.9 and for FOFLIRI + bevacizumab 13.6 ± 5.5, p<0.001. Confirmed time to progression for FOFLIRI (Group I) was 6.9 months and for FOFLIRI + bevacizumab (Group II) 10.2 months, p=0.003. In multivariate analyses (age, gender, ECOG status, site of metastatic disease, type of therapy) only significantly associated factor to outcome of treatment was type of therapy. Addition of bevacizumab to FOFLIRI showed improvement in PFS, HR=0.40, 95% CI 0.21-0.78, p=0.007. The most common side-effects in both groups were diarrhea, nausea, vomiting and neutropenia, but without statistically significant differences between groups. In Group II (FOFLIRI + bevacizumab) there were more thromboembolic events (4.5%), one intestinal perforation (2.3%), one bleeding from primary (2.3%), hypertension in four patients (9.0%).

Conclusions: Our data suggest that combination of FOFLIRI + bevacizumab is significantly better combination than FOFLIRI in term of PFS, with acceptable toxicity.

Disclosure: All authors have declared no conflicts of interest.

NEUTROPENIA AND GENDER DIFFERENCES AT LIVER-ONLY METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH OXALIPLATIN-BASED NEOADJUVANT CHEMOTHERAPY PLUS BEVACIZUMAB: IS THERE ANY IMPACT ON RESECTION RATE?

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Introduction: Combined chemotherapy (cytotoxic+biological agent) that aims to shrink liver metastases and to allow successful resection may be associated with haematological toxicity in colorectal cancer (CRC) patients (pts). In general, neutropenia is not an obstacle for resection planning but it may prolong chemotherapy period and possibly affect further steps in this potentially curative setting.

Methods: Pts with potentially resectable liver-only metastatic CRC and PS 0/1 have been selected to receive at least four induction cycles of FOFLIRI regimen (six of them XELOX) + bevacizumab, at the Institute for Oncology and Radiology of Serbia, since Sep 2008. Neutropenia and delay in chemotherapy delivery with G-CSF support (in days) were recorded. Response rate (RR) and resection rate were analysed.

Results: Forty-seven pts were assessed for resection. Thirty-eight pts received four or more cycles of FOFLIRI (six of them XELOX) + bevacizumab, nine pts received up to four cycles of the same therapy. Among these 47 pts 21 were male, 26 female, median age was 56 years, and PS 0 was recorded in 41/47 (87%) pts. Febrile neutropenia was not registered, grades 3 and 4 neutropenia were recorded in 40% of pts, (male vs female: 29% vs 50%, p=0.08). Median delay in chemotherapy administration and G-CSF consumption was 3 days (males/females:4/3). RR was 38%, both in males and females. Overall resection rate was 26% (12/47 pts), in pts 14% (95%CI:5-35%), in female pts 35% (95%CI:19-54%), p=0.18. Higher grades of neutropenia did not significantly impact resection rate: among 19 pts who experienced grade 3 and 4 neutropenia 7 pts were resected, among 26 pts with grades 0-2 neutropenia 4 pts were resected, p=0.16. At pts with neutropenia grades 3 and 4 response rate was 58%, while at pts with neutropenia grades 0-2 response rate was 19%, p=0.08.

Conclusion: It appears that moderate and severe neutropenia, although experienced in 40% of pts after the induction of four cycles of chemotherapy + bevacizumab, did not affect the planned further treatment. There was no proof of gender differences significance. These preliminary findings deserve further studies, in order to understand better prognostic and predictive factors in setting of liver-only metastatic CRC.

Disclosure: All authors have declared no conflicts of interest.
CLINICAL OUTCOMES IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH BEVACIZUMAB AND K- RAS MUTATION STATUS

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Introduction: Mutations of the K-ras gene were identified as a negative predictor of chemotherapy benefit for anti-angiogenic growth factor receptor treatment in metastatic colorectal cancer (mCRC). Previous data, from clinical trials, suggest that the clinical benefit in patients treated with Bevacizumab plus chemotherapy is independent of alterations in the Ras/Raf/MEK/Erk pathway. We were aimed to investigate the impact of K-ras mutational status in clinical outcomes – progression free survival (PFS) and overall survival (OS) – of patients with mCRC treated with Bevacizumab plus chemotherapy in a selected population.

Patients and methods: A retrospective analysis of our patient’s dataset with mCRC treated with Bevacizumab plus chemotherapy after May 2006 in our institution was performed. K-ras mutation status was analyzed by RT-PCR in Genomed (IMM) and patients were grouped as having or not K-ras mutation. The PFS and OS times were compared. Multivariate analysis was done with Cox regression model. Log-Rank test was used to determined significance (p < 0.05). We analyzed a population of 70 patients: female:44,8%,male: 55,2%. Median age of diagnosis: 63.6 years. K-ras mutation status in PFS and OS was (65,7%) patients died. The median progression free survival was 7 months (95%CI, 4.1 - 9.9). The median overall survival was 15 months (95%CI, 9.8 - 18.5). Grade 3-4 toxicity requiring delay of chemotherapy was observed in 12 (34.3%) patients: 10 (28.6%) had neutropenia and 2 (5.7%) had diarrhea.

Conclusion: Bevacizumab-B may be an efficient and safe choice in the second line for the treatment of patients with mCRC that were previously treated with oxaliplatin.

Disclosure: All authors have declared no conflicts of interest.

THE RELATION BETWEEN ENDODGIN (CD105), THROMBOSPONDIN-1 AND VEGFR-3 AND TREATMENT RESULTS IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH BEVACIZUMAB COMBINATION THERAPY

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Background: Angiogenesis is an important step in growth of malignant tumors. The relationship between efficacy and angiogenic factors such as CD105 (endoglin), thrombospondin-1 (TSP-1) and vascular endothelial growth factor receptor 3 (VEGFR-3) in patients with metastatic colorectal cancer (mCRC) treated with bevacizumab, antiangiogenic agent, combination chemotherapy was assessed.

Patients and methods: The clinicopathological data of 42 mCRC patients retrospectively analyzed. The expressions of CD105, TSP-1 and VEGFR-3 were examined in paraffin block of these patients by immunohistochemical staining.

Results: Forty two patients with a median age of 55 years (range, 29-78) were evaluated. The median follow-up was 16 months (range, 3-41). The expression of TSP-1 and VEGFR-3 were 11.9% and 19%, respectively and 46% of patients showed widespread expression of CD105. The overall response rate, PFS and OS results according to treatment-line, CD105, TSP-1 and VEGFR-3 expressions as follows: in first-line, 16-17% 5 months and not reached and in salvage therapy, 26-7% 6 and 15 months; in CD105 widespread subgroup 15.5%, 6 and 16 months and in CD105 weak staining subgroup 31.6%, 6 and 19 months; in TSP-1 positive group 9%, 6 and 13 months and in TSP-1 negative group 29.7%, 6 and 16 months; in VEGFR-3 positive group 12.5%, 6 and 15 months and in VEGFR-3 negative group 26.5%, 6 and 16 months, respectively.

Conclusion: Non-significant treatment efficacy according to expression of these angiogenic markers in patients treated with bevacizumab combination chemotherapy showed that they have no clinically applicable prognostic significance in mCRC patients. Large prospective studies were necessary to establish this relationship clearly.

Disclosure: All authors have declared no conflicts of interest.
Background: Antiangiogenic treatment with bevacizumab is a part of standard systemic therapy for metastatic colorectal cancer (mCRC). In a retrospective study, we have analysed the outcomes of therapy and prognostic/predictive factors in patients (pts) treated in two Czech cancer centres.

Patients and methods: The cohort included 238 consecutive pts treated with bevacizumab for mCRC at the Masaryk Memorial Cancer Institute and at the Thomayer University Hospital, Czech Republic. The following potential prognostic/ predictive factors were evaluated: age, gender, tumour grade, number of metastatic sites, associated chemotherapy regimen, presence/absence of KRAS mutation, and preexisting or therapy-induced hypertension.

Results: Median age of pts treated with bevacizumab as a part of first-line systemic therapy was 68 years. The progression-free survival (PFS) and overall survival (OS) were 11.3 months and 30.6 months, respectively. ORR was 45.6% with 12% CEs and disease stabilisation occurred in 29% of pts. Higher grade and/or number of metastatic sites were adversely associated with both PFS and OS. KRAS was not predictive of PFS but was a strong favourable prognostic factor for OS due to the possibility of subsequent therapy with cetuximab (43.8 vs. 27.5 months, p=0.031). Toxicity profile was as expected but thromboembolic events occurred in as many as 11% of pts 65 years or older. Preexisting or de novo hypertension was not associated with treatment outcomes.

Conclusion: Outcomes of ‘real-life’ pts with mCRC are comparable to those achieved in clinical trials. Thromboembolism emerges as the most significant toxicity in elderly mCRC pts treated with bevacizumab. Sequential targeted therapy improves survival in mCRC but is currently an option only for pts with KRAS wt tumours.

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All other authors have declared no conflicts of interest.

IMPLICATIONS OF EXPRESSION MARKERS OF APOPTOSIS IN COLORECTAL CANCER WITH METASTASIS IN LIVER

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Aim: To demonstrate correlation dependence between levels of expression of p53 and bcl-2 in patient's with colorectal cancer (CRC) metastasis in liver and the results of using chemotherapy.

Materials and methods: Study was of 85 CRC patients with metastasis in liver, 1st group (n=32) received chemotherapy by the FOLFIRI regimen (irinotecan-180 mg/m², leucovorin-200mg/m², fluorouracil-400mg/m²) iv. in 1st day, then 5FU – 2.4 – 3.0mg/m² 24 hours iv. in following days, 2nd group (n=25) received regional endovascular chemotherapy (REICH) with 5-fluorouracil– 1000 mg/m² daily during 72 hours and oxaliplatin 100 mg/m² daily during 16-18 hours on the fourth day, 3rd group (n=25) received capcitabine (Xeloda; 3500mg/m²). All patients were subject to immunohistochemical analysis of expression of protein p53 and bcl-2 by IUB (Dako Cytomation).

Results and discussion: results showed that the highest level of protein expression of mt p53 in tissue of primary tumor (n=20) was found in moderately differentiated adenocarcinoma. In high-grade differentiated adenocarcinoma the expression p53 occurs in 52.0%, in moderately differentiated adenocarcinoma in 41.66%. Immunohistochemical analysis of primary tumor CRC showed 35 (42.1%) cases of gene expression of mt p53, of them in 10 (12.04%) showed high expression of the given oncogene. Absence of gene expression mt p53 was observed in 57.83% patients. Expression of bcl-2 was negative. Analysis of results showed that the conducted treatment results were dependent on patient’s phenotype: Using FOLFIRI showed full treatment results were dependent on patient phenotype. Using FOLFIRI showed full remission and disease control was achieved in 32.8% patients, 24% of them were refractory to standard chemotherapy and not available to biologic novel agents. We evaluated the outcomes of mitomycin-C/5-FU/capcitabine in patients with
metastatic colon cancer receiving previously oxaliplatin/5-fluorouracil/FU/leucovorin (mFOLFOX6) adjuvant chemotherapy and mFOLFOX6 were used. Methods We retrospectively analyzed 46 patients who had received mitomycin-C5FU/leucovorin between March 2008 and December 2009. All patients had failed prior first-line and second-line therapy containing oxaliplatin, trinitocan and 5-fluorouracil.

Results: The median age of patients was 57.0 years (range, 34.0-76.0) and median ECOG PS was 1 (0-2). In all patients, complete or partial response was not observed and stable disease was observed in 19 patients (41.3%). The median duration of follow-up was 29.14 weeks (range 7.71-87.29 weeks). The median progression free survival (PFS) was 10.14 weeks (95% CI: 8.45-11.83) and the median overall survival (OS) was 38.00 weeks (95% CI: 32.28-43.72). Grade 3 and 4 hematologic toxicities included neutropenia in 5 patients (10.8%) and thrombocytopenia in 4 patients (8.8%). Grade 3 or 4 non-hematologic toxicities included nausea and vomiting in 2 patients. There were no treatment related deaths.

Conclusion: The combination regimen of mitomycin-CSFU/leucovorin showed marginal activity and tolerable toxicity profiles in heavily pretreated metastatic colorectal cancer patients.

Disclosure: All authors have declared no conflicts of interest.

691 MULTICENTER PHASE II STUDY OF FOLFOX6 AS NEOADJUVANT CHEMOTHERAPY FOR PATIENTS WITH UNRESECTABLE LIVER-ONLY METASTASES FROM COLORECTAL CANCER IN JAPAN; ROOF STUDY

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Background: A phase II multicenter cooperative study was conducted in 38 medical institutions using modified FOLFOX6 (mFOLFOX6) as neoadjuvant chemotherapy from January 2008 to Jun 2009.

Patients and methods: Patients with liver-only metastases from colorectal cancer deemed not operable by surgeons received mFOLFOX6 (oxaliplatin 85mg/m2, bolus 5-FU 400mg/m2, leucovorin 400mg/m2 day1 followed by 46-hour infusion 5-FU 2.4mg/m2) as neoadjuvant therapy for 6-8 cycles. Unresectable liver metastases was defined as >4 metastatic tumors and/or a tumor >5 cm in maximum diameter. Patients were reassessed for resectability after 6 cycles of mFOLFOX6. Surgery was carried out 3-6 w after chemotherapy. Primary end point was macroscopic curative surgery including liver resection.

Results: 36 patients (23M/13F, ECOG PS 0-1) were enrolled. Median age of the patients was 62.5 years, 78% (28 patients) had 5 or more metastatic tumors, 53% (19 patients) had metastatic tumors in over 5cm diameter. Modified FOLFOX6 regimen was safely administered resulting in 18 PRs (50%), 12 SDs, and 4 PDs. There was no grade 3/4 neurotoxicity. Fifteen patients (42%) underwent surgery (R0;13, R1;2). There were no treatment-related deaths. 31 patients are alive after a median follow-up of 12 months (range 3-24 months).

Conclusion: Our data suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a portion of patients initially not judged to be optimally resectable. With liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a portion of patients initially not judged to be optimally resectable.

Disclosure: All authors have declared no conflicts of interest.

692 COLONRECTAL (CR) RESECTABLE LIVER METASTASES: LONG-TERM PATIENT SURVIVAL AFTER PREOPERATIVE TRANSTHORACAL CHEMOEMBOLIZATION TACE WITH OXALIPLATIN FOLLOWING HEPATIC RESCCTION (HR)

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Background: HR is a standard treatment option in resectable CR liver metastases patient. Very expensive multicomponent treatment has allowed raising recurrence-free survival to 6-9%.

Purpose: To evaluate the CR resectable liver metastases treatment included preoperative TACE with oxaliplatin following HR.

Material and methods: A prospective nonrandomized trial, including 66 synchronous and metachronous CR resectable liver metastases patients, has been completed. Resectability criteria: removal of all metastases, portal vein, more than 2 hepatic vein and vein cava inferior invasion absence. HR has been performed in the group 1 (n=40), average age 59 years, 25 men, 15 woman. TACE with 50.100 mg oxaliplatin following HR in 4-6 weeks has been worked out in carried out in group 2 (n=10, 58, 28%). TACE with 30-50 mg doxorubin following HR in 4-6 weeks has been conducted in group 3 (n=16, 36, 8/8).

Results: Median and 3-year recurrence-free survival (RFS) has amounted to 13, months and 25,7±2.9% in group 1, 35,7 months and 38,3±4,1% in group 2, 13,8 months and 6,3±6.1% in group 3, respectively (p=0.017). RFS was higher in group 2 versus group 1 (p=0.04) and group 5 (p=0.003). Median, overall 3-and 5-year survival has amounted to 31,6 months, 46,8±6,9% and 37,1±8,0%, respectively in group 1. Median hasn’t obtained, overall 3- and 5-years survival have amounted 77,1±14,4% in 31,4±17,7% in group 2. Median, overall 3- and 4-years survival have amounted 29,5 months, 41,7±12,9% ±16,6±10,5%, respectively in group 3. Statistically significant differences of overall survival haven’t obtained (p=0.13).

Conclusion: Using TACE with oxaliplatin and HR in CR resectable liver metastases patients has improved recurrence-free survival. The III phase of clinical trial is planned.

Disclosure: All authors have declared no conflicts of interest.
Materials and methods: Patients to be treated with sphincter-preserving operations were divided into 3 groups. 1st group included 29 (35.4%) patients with tumor, located at 10-15 cm away from the edge of anorectal line. Patients from this group were treated with anterior resection of rectum with anastomosis and standard lymph nodes dissection. 2nd group had 18 (21.9%) patients with the tumor, located at 9 cm or lower away from anorectal line. These patients were treated with low anterior resection with anastomosis and extended lymph nodes dissection. The (control) 3rd group enrolled 35 (42.7%) patients with various location of the tumor in rectum. Control group patients were treated by abdominal resection of rectum with standard lymph nodes dissection (19 patients with pulling proximal parts of colon into anal canal and 16 patients with pulling sigmoid colon into anal canal). Reconstrcutive recovery stage was carried out as one step in 36 patients and in two steps in 26 patients.

Results: There are significance differences regarding the short term effects of these three groups, such as post-operative complications: suppurator of post-operative wound, incompetence of anastomosis, acute adhesive intestinal obstruction, bleeding, necrosis and retraction of pulling colon. Two study groups were much better than the control group. The long term effects manifesting by three year survival rate in group I, II and III were 82.8% (p=0.0084), 77.8% (p=0.091) and 65.7% respectively. Quality of Life scales are higher for group I and II than group III.

Conclusion: Low anterior resections with extended lymph nodes dissection demonstrated to be superior to abdominal resection of rectum in following indices: decrease of the local recurrences, prolongation of life duration, and improvement of physical and psychological status.

Disclosure: All authors have declared no conflicts of interest.

**986 IMPACT OF ADJUVANT CHEMOTHERAPY ON SURVIVAL OF PATIENTS WITH STAGE II COLON CANCER: RETROSPECTIVE STUDY**

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Background: The survival benefit of 5-FU-based adjuvant chemotherapy for stage II colon cancer patients have led some physicians to recommend adjuvant chemotherapy for their stage II colon cancer patients.

Objectives: To investigate effect of 5-FU-based adjuvant chemotherapy in stage II colon cancer patients (pts) as regards disease-free survival (DFS), overall survival (OS) and to correlate treatment outcome in relation to different clinicopathological features.

Materials and methods: Data of stage II colon cancer pts (273 pts) who received adjuvant chemotherapy in Oncology Unit of MRR Alex. Univ. from 01/1995 to 12/2004 were including: (Age, Sex, Family history, Tumor histology, Tumor marker (CEA), Metastasis (M), TNM, Histological grade, Tumor size, Absence or presence of lymph nodes metastasis, Pt’s comorbidities). The pts were divided into two groups: Group A received 5-FU (5-fluorouracil) (2400 mg/m2 over 42 HAI q2w) in a single center (UZ Brussels) was analyzed after a median follow up of 55 months (range 82-6).

Results: Pts presented with symptoms duration less than 6 months had better OS at 3 years. Pts received 6-cycles had better DFS. Intraosseous injection was accompanied by lower OS at 3 and 5 yrs and DFS at 3 yrs. Vascular invasion had an impact on both DFS and OS at 3 and 5 yrs. Higher level of CEA was accompanied by lower DFS and OS at 3 and 5 yrs. Pts with poorly differentiated tumors had lower DFS. For all pts, DFS at 3 and 5 yrs were 72.2% (57.1%), while OS at 3 and 5 yrs were (86.1%) and (73.6%) respectively.

Conclusion: There is no improvement in OS, But DFS was better with adjuvant chemotherapy. Pts with high risk features get benefit from adjuvant chemotherapy. Consider co-morbidities and tolerance to chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

**988 CLINICAL OUTCOME OF PATIENTS TREATED WITH HEPATIC ARTERIAL INFUSION OF OXALIPLATIN AND L-FOLIC ACID MODULATED 5-FLOUOROURACIL FOR INOPERABLE COLORECTAL CANCER LIVER METASTASES, A SINGLE CENTER EXPERIENCE**

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Background: Despite the progress made in the treatment of metastatic colorectal cancer (CRC), 5-year survival rates for patients (pts) with inoperable liver metastases (LM) remains poor. Encouraging anti-tumor activity has been reported with hepatic arterial infusion (HAI) of oxaliplatin (OXA) containing chemotherapy but long-term outcome of pts treated with this modality remains underestimated at present.

Methods: The clinical outcome of pts with unresectable CRC-LM treated with HAI of OXA in combination with l-folic acid (400 mg over 2-6 h iv) modulated continuous HAI of 5-fluorouracil (cis-FU/FA) (2400 mg/m² over 42 HAI q2w) in a single center (UZ Brussels) was analyzed after a median follow up of 55 months (range 82-6).

Results: 23 Caucasian pts (17M/6F, median age 56.7 (range 28-79) at initiation of HAI were identified. Characteristics: 11 rectum, 12 colon; 3 pts received adjuvant chemotherapy, 7 pts received oxali-HAI at 1st line and 16 as 2nd-line chemotherapy. All except 2 hepatic artery catheters were placed during laparoscopy. A median of 7.2 (range 2-15) cycles of OXA-containing chemotherapy were administered. Cystic bile duct dilatation with arterio-biliary shunt (gr1) was observed in one pt. The most frequent treatment related adverse events were: abdominal pain (9 pts), nausea, increased liver enzymes (n= 5 pts), diuodenal ulcer (1 pt), sensorial polyneuropathy (8 pts), and reversible toxic interstitial pneumonitis (1 pt). There were no gr4 or 5 AE's. Reasons for stopping HAI were: catheter thrombosis in 10 pts (43%), unacceptable toxicity in 5 (22%) and PD in 3 (13%). Objective response (RECIST) were: 1 CR, and 18 PR (BORR = 82%), and 4 SD. Median TTP from initiation of HAI: 7.4 mths (95% CI 6-8.9); median OS from diagnosis of stage IV disease: 39 mths (95% CI 30-47) and from the initiation of HAI: 23 mths (95% CI 12 - 35).

Conclusion: HAI of OXA plus cis-FU/FA is feasible and results in a favorable survival of pts with unresectable CRC-LM. This experimental treatment is associated with specific but manageable toxicity. Randomized clinical trials on OXA-HAI in this population of pts seem warranted.

Disclosure: All authors have declared no conflicts of interest.

**987 RANDOMIZED PHASE II STUDY OF HEPATIC ARTERIAL INFUSION WITH OR WITHOUT ANTINEOPLASTONS AS ADJUVANT THERAPY AFTER HEPATECTOMY FOR LIVER METASTASES FROM COLORECTAL CANCER**


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Background: Hepatic recurrence occurs in a high rate after hepatectomy for patients with colorectal metastasis to the liver. Therefore, hepatic arterial infusion chemotherapy (HAI) has been applied as an adjuvant therapy after hepatectomy. However, HAI is less effective against extra-hepatic recurrence. Antineoplastons (AS2-1 and AS2-10) are naturally occurring peptides and amino acid derivatives found in human blood and urine. Sodium phenylacetate is the main component of AS2-1 and A10. The small peptides reportedly control neoplastic growth and have minimum adverse effects. It seems to be reasonable to apply systemic administration of antineoplastons in addition to HAI after hepatectomy in colorectal metastasis to the liver. This randomized phase II study compares the efficacy of hepatic arterial infusion with or without antineoplastons as postoperative adjuvant therapy for colorectal metastasis to the liver.

Patients and methods: A total of 65 patients who underwent hepatectomy, thermal ablation or their combination for liver metastases from colorectal cancer enrolled between 1998 and 2004 from Kurume University hospital. The patients were randomly assigned to receive systemic antineoplastons (infusion A10 followed by peroral AS2-1) plus HAI using 5-fluorouracil (group A) or HAI alone (group B) by the number of metastases and presence of extra-hepatic metastasis at the time of or before operation. The primary endpoint was mode and extent of recurrence, and secondary endpoints were cancer-specific survival, disease-free survival, rate of re-surgical treatment and adverse effects.

Results: Thirty two patients were randomly assigned to group A and 33 to group B. The cancer-specific survival rate in the group A was higher than that in the group B. Although the disease-free survival rates were similar between the groups, the rate of single organ recurrence and re-surgical treatment was higher in the group A. In addition, the extent of recurrent tumors in the group A tended to be larger and more metastatic. The major adverse effects of antineoplastons were fullness of the stomach and phlebitis. However, no additional toxicity such as bone marrow suppression, liver dysfunction and renal dysfunction was found in the group A.

Conclusion: Antineoplastons appears to be useful as an adjuvant therapy in addition to hepatic arterial infusion after hepatectomy in colorectal metastases to the liver.

Disclosure: All authors have declared no conflicts of interest.
Fluorouracil (5FU) based chemotherapy is an effective treatment for patients with hepatic metastases from colorectal cancer. This review investigated the utility of 5FU in patients with metastases confined to the liver.

Methods: Patients recruited in three first-line metastatic colorectal cancer studies were considered for inclusion. Patients eligible for inclusion had metastatic colorectal cancer confined to the liver. Patients received a single implantation of SIR-Spheres® and ongoing infusional 5FU based chemotherapy. Chemotherapy was administered until complete response, resection, disease progression or unacceptable toxicity. Response rate (RECIST), progression-free survival (PFS), overall survival (OS) and safety were reviewed.

Results: 31 patients were accrued between 1999 and November 2009. Median follow-up is 5.5 years; 16 patients received systemic 5FU chemotherapy, 15 received systemic FOLFOX chemotherapy. Best response was complete in 5 patients (16%), partial in 24 (75%) and stable in 3 (9%). Median PFS was 15.2 months, median PFS in the liver was 16.4 months, median OS was 30.7 months. 7 patients remain alive with a median follow up of 4.7 years (range 0.6 to 7.7).

1 patient died of radiation induced liver disease without documented progression of disease.

Conclusion: The combination of RE and 5FU based chemotherapy appears effective in controlling liver metastases from colorectal cancer. This benefit of multi-modality therapy was reflected in the response rate, PFS and OS when compared with historical controls in the absence of extracranial disease.

Disclosure: All authors have declared no conflicts of interest.

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Optimal Schedules of Concomitant Chemoradiotherapy (CRT) with S-1

Preoperative concomitant CRT consisting of radiation (RT) and 5-fluorouracil-based chemotherapy improves the local control of locally advanced rectal cancer (LARC), but the optimal combination regimen is a matter of controversy. S-1, a novel oral fluoropyrimidine, has demonstrated comparable therapeutic efficacy with UracilTeperafur (UFT) plus leucovorin in advanced colorectal cancer. The aim of this preclinical study was to identify the optimal sequencing to cause potent radiosensitization by S-1.

Purpose: To evaluate the efficacy and safety of preoperative concurrent cetuximab, capecitabine and radiotherapy in the treatment of resectable locally advanced rectal cancer (LARC).

Methods and materials: We conducted a pilot trial to assess pathological complete response, tumor downstaging, safety of cetuximab (Anti-EGFR) given weekly for 7 cycles, starting with an initial dose of 400 mg/m2 one week (day -6) before radiation therapy, followed by 250 mg/m2/week on days 1,8,15,22,29 and 36 of radiation therapy in addition to Capecitabine at a dose of 1650 mg/m2 (divided in 2 doses, q12hours), daily throughout the 5.5 week course of preoperative irradiation, starting with the first day of radiation and ending with the last day of radiation. Preoperative radiotherapy was given to a total dose of 45Gy in 25 fractions over 5 weeks using a 4-field box technique followed by a tumor bed boost of 5Gy in 3 fractions (1.6Gy daily fractionation) using a 3-field technique. The patients then had rest for 6-8 weeks before proceeding with surgery.

Results: From June 2008 till June 2009, a cohort of 15 patients with median age of 52 years, 10 males and 5 females were enrolled. 73.3% had ECOG performance status of 1. 14 patients were K-RAS WILD type ( retrospective analysis). Clinical staging at presentation was T3, N1, N2 disease found in100%, 80%, and 29% by endoscopic ultrasound respectively. In 26.7% the tumor was fixed. Eight patients had tumors less than or equal to 5 cm distant from the anal verge. 15 patients had surgery, sphincter preservation was achieved in 11 patients (73.3%), with pathological complete remission rate of 13.3%. Tumor and nodal down staging occurred in 60%, 53.3% respectively. One patient was found to be metastatic at surgery. Grade 3 toxicities were mainly diarrhea (29%), skin toxicities (13.4%). With median follow up of 13 months ,13 patients(86.6%) are relapse free.

Conclusion: The addition of cetuximab to preoperative capecitabine and radiation therapy is feasible with encouraging results; a further larger randomized trial of this combination is warranted.

Disclosure: S. Bazarbashi: Research Grant from Merck Sorono pharma to fund the study

All other authors have declared no conflicts of interest.

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Metastases after Yttrium-90 radioembolization

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Introduction: Intra-arterial Yttrium-90 radioembolization is a novel treatment modality for metastatic colorectal cancer (CRC) patients with unresectable, chemorefractory, liver dominant disease. In this pilot study we assess the influence of limited extrahepatic disease on clinical outcome.

Methods: For this study all consecutive patients with CRC liver metastases, progressing upon standard systemic treatment, treated with Yttrium-90 radioembolization in our hospital in 2009, were retrospectively analyzed. Outcome parameters were response of liver lesions according to RECIST (partial response, stable or progressive disease), extrahepatic tumor response defined as early (within 3 months after treatment) change in size or number of extrahepatic lesions (stable or progressive disease) and survival. Response was evaluated using computed tomography (CT) or magnetic resonance imaging (MRI) at baseline, and at one and three months after treatment.

Results: A total of 9 patients completed treatment for this study. Six patients presented with limited extrahepatic disease 14 male, 2 female; mean age, 55 yrs; mean tumor load 17.3% treatment, whole liver n=2, lobar in 2 temp n=2, right lobe only n=2) and three patients had liver-only disease (1 male, 2 female; mean age, 60 yrs, mean tumor load 16.0%; treatment, whole liver n=2, right lobe only n=1). Response of liver lesions in the extrahepatic group was stable disease in 4 patients, partial response in 1 patient and 1 patient was lost to follow up. Response of liver lesions in the liver-only group was stable disease for all 3 patients. At three months follow up, progression of extrahepatic disease was observed in 3/6 patients in the extrahepatic group and 0/3 in the liver-only group. In total three patients died during follow-up, all of whom had extracranial lesions at baseline.

Conclusion: In this small series we observed and reported for the first time unexpected rapid tumor growth of extrahepatic lesions after Yttrium-90 radioembolization, while liver lesions responded. We hypothesize that radioembolization may induce a systemic response which triggers growth of extrahepatic lesions, such as release of angiogenic factors.

Disclosure: All authors have declared no conflicts of interest.

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Pilot trial of preoperative chemoradiotherapy using capecitabine, external beam radiation and cetuximab followed by definitive surgery in patients with localized (non-metastatic) rectal cancer

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Purpose: To evaluate the efficacy and safety of preoperative concurrent cetuximab, capecitabine and radiotherapy in the treatment of resectable locally advanced rectal cancer (LARC).

Methods and materials: We conducted a pilot trial to assess pathological complete response, tumor downstaging, safety of cetuximab (Anti-EGFR) given weekly for 7 cycles, starting with an initial dose of 400 mg/m2 one week (day -6) before radiation therapy, followed by 250 mg/m2/week on days 1,8,15,22,29 and 36 of radiation therapy in addition to Capecitabine at a dose of 1650 mg/m2 (divided in 2 doses, q12hours), daily throughout the 5.5 week course of preoperative irradiation, starting with the first day of radiation and ending with the last day of radiation. Preoperative radiotherapy was given to a total dose of 45Gy in 25 fractions over 5 weeks using a 4-field box technique followed by a tumor bed boost of 5Gy in 3 fractions (1.6Gy daily fractionation) using a 3-field technique. The patients then had rest for 6-8 weeks before proceeding with surgery.

Results: From June 2008 till June 2009, a cohort of 15 patients with median age of 52 years, 10 males and 5 females were enrolled. 73.3% had ECOG performance status of 1. 14 patients were K-RAS WILD type ( retrospective analysis). Clinical staging at presentation was T3, N1, N2 disease found in100%, 80%, and 29% by endoscopic ultrasound respectively. In 26.7% the tumor was fixed. Eight patients had tumors less than or equal to 5 cm distant from the anal verge. 15 patients had surgery, sphincter preservation was achieved in 11 patients (73.3%), with pathological complete remission rate of 13.3%. Tumor and nodal down staging occurred in 60%, 53.3% respectively. One patient was found to be metastatic at surgery. Grade 3 toxicities were mainly diarrhea (29%), skin toxicities (13.4%). With median follow up of 13 months ,13 patients(86.6%) are relapse free.

Conclusion: The addition of cetuximab to preoperative capecitabine and radiation therapy is feasible with encouraging results; a further larger randomized trial of this combination is warranted.

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All other authors have declared no conflicts of interest.
Conclusions: The broad timing of combination schedule for CRT with S-1 must be a great advantage for clinical setting. These results suggest that S-1 is a promising new candidate in combination with preoperative RT in LARC.

Disclosure: All authors have declared no conflicts of interest.

THE TREATMENT OF METASTATIC RECTAL CANCER (MRC): A REVIEW OF THE MULTIDISCIPLINARY APPROACH AT THE OTTAWA HOSPITAL CANCER CENTRE (TOHCC)

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Background: There is significant controversy surrounding the management of surgically resectable MRC. The use and timing of neoadjuvant chemotherapy, pelvic radiation, and relative risks and benefits of a combined surgical resection are areas of debate among surgeons, medical, and radiation oncologists. The TOHCC multidisciplinary Cancer Conferences (MCC) provide an opportunity to discuss these cases and propose treatment plans for these patients.

Methods: We conducted a retrospective chart review of all the cases of MRC which were discussed at MCC at the TOHCC from November 2007 until October 2009. Information collected included patient demographics, site of metastases, the treatment they received prior to their case being discussed at MCC, the treatment plan discussed at MCC, treatment actually administered post MCC discussion, and patient outcome at 6 months.

Results: Forty-two patients with MRC were reviewed. The most common sites of metastases were liver (45.2%) and lung (31%). Once diagnosed with metastatic disease, prior to the MCC, patients had received the following treatments alone or in combination: chemotherapy (neoadjuvant: 38.1%; adjuvant: 23.8%; palliative: 28.6%), radiotherapy (neoadjuvant: 14.3%; adjuvant: 23.8%; palliative: 28.6%), chemotherapy (neoadjuvant: 38.1%; adjuvant: 23.8%; palliative: 28.6%), radiotherapy (neoadjuvant: 14.3%; adjuvant: 23.8%; palliative: 28.6%) and surgery (31.0%), 10 (23.8%) of which underwent a metastectomy.

Conclusions: There is no standardized approach to the management of MRC. Given its complexity, many cases are reviewed at MCC, which allow coordination for multidisciplinary care of these patients. Furthermore, following discussion of their case at MCC rounds, a significant proportion of patients with metastases were treated for cure. The results of this study suggest that in a majority of cases, the recommendations brought forth are acted upon. Given that these meetings have a significant impact on the treatment plan and outcome of patients with MRC, they should represent the standard of care when treating this disease.

Disclosure: All authors have declared no conflicts of interest.

LONG TERM SURVIVAL IN ADVANCED RECTAL CANCER AND THE EFFECTS OF TREATMENT METHOD

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Introduction: There are around 950 000 new cases of colorectal cancer in the world each year with about 500 000 patients dying [3]. According to the Cancer-Registry of Ukraine in 2007 there were 9163 rectal cancer (RC) [1]. Treatment of RC is increasingly complex and the role of combined therapy remains a matter of debate [1, 2]. A large proportion of advanced RC (ARC) show high mortality, as the low efficiency of existing methods necessitate the search for new standards of diagnosis and treatment of RC.

Materials and methods: A retrospective analysis was made of 321 cases of ARC with stages III (Dukes-MAC C2-C4-N1-2M0-2C0) and IV (Dukes-MAC D, T4a, N0-N2,N,M1) treated in the Transcarpathian region in the periods 1994-1999, and 2000-2004 combined (Surgery+ Radiotherapy) and complex (Radiotherapy+Surgery+Chemotherapy) methods.

Results: In 1994-1999 there were 158 cases of ARC, in stage III–93, in stage IV–65. In 2000–2004 years were 163 cases of ARC on stage III–118, stage IV–45. Neoadjuvant radiotherapy in dose 25 Gy or in dose 40-60 Gy was standard. Chemotherapy was carried out under the Mayo-regimen in most cases, but use new drugs (Xeloda, Oxaliplatin) in some cases 2000-2004. Standard surgery procedures were performed effectively the same in all periods without liver surgery. Long term results are presented in the Table 1. Table 1 Long term results of treatment of ARC.

Conclusions: I. Correct selection of treatment strategy and individual approach allows for the improvement of the results of 5-year survival. 2. In III stage - choice of treatment is a matter of debate. 3. In IV stage - the application of new generations of drugs in complex treatment help to achieve a 5-year survival of 25%.


Disclosure: All authors have declared no conflicts of interest.

CIRCULATING TUMOR CELLS (CTCS) IN LOCALLY ADVANCED RECTAL CANCER (LARC) PATIENTS UNDERGOING NEOADJUVANT TREATMENT

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Background: CTCs detected at baseline and at disease-evaluation time-point during treatment seems to be an independent prognostic factor in metastatic colorectal cancer while its role in early stages is under investigation. Nowadays no data have been published in patients affected by LARC. Aim of the study: To investigate the role of CTGs in patients with LARC undergoing neo-adjuvant chemotherapy (CT-RT) followed by curative resection. Primary end-points are evaluation of CTCs rate, correlation of CTCs at baseline with main patient characteristics, disease-free and overall survival and correlation of serial CTCs sampling with outcome.

Materials and methods: In a prospective single institution study, CT-4 and/or N+ rectal cancer patients staged by rectal ultrasound and/or pelvic MRI and chest-abdomen CT scan, received capecitabine (825 mg/mq, orally, tid 14/21 days). Surgical treatment comprises low anterior resection or abdomino-perineal resection with total mesorectal excision. CTCs are detected at baseline (t0), after neoadjuvant therapy, before surgery (t1), within 7 days after surgery (t2), and at 6-month follow-up (t3) and are enumerated with CTCs is defined as the number of ct-negative 1000-1250 mg/mq, orally, tid 14/21 days). Surgical treatment comprises low anterior resection or abdomino-perineal resection with total mesorectal excision. CTCs are detected at baseline (t0), after neoadjuvant therapy, before surgery (t1), within 7 days after surgery (t2), and at 6-month follow-up (t3) and are enumerated with determination of circulating tumor cells (CTCs) in blood samples.

Results: From July 2008 to February 2010 40 patients (25 M; 15 F; median age 63 y=range 44-83) underwent 100 samplings; 33 completed CT-RT and therefore underwent t1 and t2 sampling. Nowadays 19 patients have completed t3 sampling. At t1, t2, t3 and t4 20(50%), 14(35%), 13(33%) patients respectively presented at least 1 CTC (p=0.07 t0 vs t2, Mc Nemar p value). Among the 19 patients who underwent t3 sampling no CTCs were detected. The median of CTCs detected was 1 CTC for t0 as well as for t1 and t2. CTCs ≥ 1 are present in 22% of our population tested at baseline. It seems that noadjuvant CT-R followed by radical surgery has an impact on CTCs reduction. However, these assumptions need to be confirmed by further data. Recruitment is ongoing.

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LOCAL RECURRENTITY OF RECTAL CANCER IN A DEVELOPING COUNTRY: HOW TO MANAGE?

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Background: Several questions arise in the management of local recurrence of rectal cancer: 1. How to select patients who may benefit from resection? 2. When neoadjuvant treatment is still possible, is it useful to give preoperative radiation or chemotherapy? 3. Is it useful to give preoperative radiation or chemotherapy?
Results: 14 cases of local recurrence were found, i.e. 12.4%. The location of the initial primary tumor was the rectum, respectively, in peritoneal, 10 cases (70%); the middle rectum, 6 cases (42%); the lower rectum in 4 cases (28%) and in 4 cases level or upper rectum (28%). Recurrence occurred within an average of 21.4 months, with a median ranged from 6 months - 5 years (50% in the first year, 64% 2 years, 12 of RLR were clinically symptomatic (86%). Confirmation of diagnosis was based on rectoscopy + biopsy because of suspected lesion on CT scan or high level on ACE (9 cases: 64%). A neoadjuvant treatment of RLC was made in two cases. Surgical management was performed on all cases. Only three patients had a curative resection.

Conclusion: The occurrence of RLR is fraught with consequence, the selection of patients for surgery with curative intent is crucial in its management. Prevention must be central in the initial management of rectal cancer. Practices must be better defined to provide quality removal optimum and reduce the incidence of RLR.

Disclosure: All authors have declared no conflicts of interest.

OUTCOME OF BRAIN METASTASES FROM COLORECTAL CANCER; A SINGLE INSTITUTE EXPERIENCE

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Background: The evolution of new chemotherapeutic agents has prolonged survival of patients with metastatic colorectal cancer and showed an increased incidence of uncommon metastatic sites like brain. The aim of this study was to evaluate trends of presentation and the efficacy of different treatment strategies in management of this rare metastatic site.

Methods: Patients with brain metastases from colorectal cancer treated in our Institute of Oncology between January 2000 - June 2009 were identified. The baseline demographic and histopathological characteristics were evaluated retrospectively. All patients had solid brain metastases without leptomeningeal carcinomatosis.

Results: A total of 14 patients (8 male, 6 female) with median age of 60 years (range: 43-72 years old) were identified. Median follow-up time was 28 months. 64 % had extracranial metastases at time of diagnosis. The most common site of metastases at presentation was liver (28.4 %) followed by bone (14 %) and lung (7 %). Primary site of tumor was sigmoid colon (57 %), rectum (28 %) and cecum (14 %). Primary tumor tended to be in more advanced stage (T4: 50 %, T3: 28 %, Tx: 22 %). Only one patient presented with brain metastases as first site of progression without any extracranial metastases. The most common site of metastases extracranial metastases was lung (49 %), 8 patients had solitary metastases while the rest were multiple. Nine patients had undergone surgery for brain metastases and followed by whole brain radiotherapy. Five patients were treated with radiotherapy without surgery due to multiple metastases. Two patients in surgery group and two patients in radiotherapy only group received chemotherapy (mainly irinotecan based) after detection of brain metastasis. The median time interval between first cancer diagnosis and brain metastasis was 26 months and mean overall survival (OS) rate for the whole patient group was 54 months. The mean OS rate for patients in surgery group was 62 months and 36 months for the rest of the patients (p>0.05).

Conclusions: Despite the recent developments in systemic treatment of metastatic colorectal cancer, survival after brain metastasis has not improved much over time. High rates of extracranial disease and small number of patients receiving systemic therapy after brain metastases limits the development of new strategies. In our study, although not statistically significant, there was a trend towards better survival rate for patients who had undergone surgery for brain metastases. However better systemic control of extracranial metastases still remains to be the cornerstone of management with brain metastases.

Disclosure: All authors have declared no conflicts of interest.