P.01 THE EFFECTS OF CALCIUM AND VITAMIN D ON THE COLORECTAL CANCER

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Background: Higher intake of calcium and vitamin D has been associated with a reduced risk of colorectal cancer in epidemiologic studies and polyp recurrence in polyph-prevention trials. However, randomized-trial evidence that calcium with vitamin D supplementation is beneficial in the primary prevention of colorectal cancer is lacking.

Method: We conducted a randomized, double-blind, placebo-controlled trial involving 5,282 postmenopausal women from Women's Health Initiative centers: 2,176 women received 500 mg of elemental calcium as calcium carbonate with 200 IU of vitamin D3 twice daily (1080 mg of elemental calcium and 400 IU of vitamin D3) and 2106 received a matching placebo for an average of 5.0 years. The incidence of pathologically confirmed colorectal cancer was the designated secondary outcome. Baseline levels of serum 25-hydroxyvitamin D were assessed in a nested case-control study.

Results: The incidence of invasive colorectal cancer did not differ significantly between women assigned to calcium plus vitamin D supplementation and those assigned to placebo (67 and 66 cases; hazard ratio, 1.08; 95 percent confidence interval, 0.96 to 1.21; p=0.42), and the tumor characteristics were similar in the two groups. The frequency of colorectal-cancer screening and abdominal symptoms was similar in the two groups. There were no significant treatment interactions with baseline characteristics.

Conclusion: Daily supplementation of calcium with vitamin D for five years had no effect on the incidence of colorectal cancer among postmenopausal women. The long latency associated with the development of colorectal cancer, along with the seven-year duration of the trial, may have contributed to this null finding. Ongoing follow-up will assess the longer-term effect of this intervention.

P.02 FURTHER CLINICAL EVIDENCE SUPPORTING USE OF MSEPT9, AS A TUMOR MARKER FOR EARLY DETECTION OF COLORECTAL CANCER IN BLOOD PLASMA

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Objectives: Colorectal cancer (CRC) screening has a low compliance rate, although the prognosis for colorectal cancer patients is more likely to be favorable when the disease is detected early. The blood-based Septin9 test is a potential new alternative for patients not willing to accept a screening colonoscopy or perform FOBT testing. Since the discovery of the mSPT9 tumor marker, seven independent studies on more than 3,000 patient plasma samples have been reported which demonstrate that the detection of methylated DNA within the SEPT9 gene (mSEPT9) in blood plasma is strongly associated with the presence of CRC. A single blood sample, sufficient for analysis of mSPT9, can be taken at a local physician’s office then analyzed by a diagnostic laboratory or clinical testing facility. Screening experts believe that such a blood-based test will increase compliance to CRC screening. Further studies are ongoing including the prospective collection of approximately 7500 individuals undergoing screening for CRC in the U.S. and Germany. The main objectives of this clinical investigation, called PRESEPT, are to determine the performance of the Septin9 test for identification of CRC in a screening population and to demonstrate the health economic benefit of Septin9 as a screening test. To further determine the characteristics of the Septin9 test in the clinical routine we have performed an additional clinical study using an assay optimized for ease of clinical use and workflow robustness. Here we present an update on current clinical data, showing evidence in support of this new screening method.

Method: The Septin9 test detects CRC-derived, cell-free DNA in blood plasma. DNA is extracted from human plasma, bisulfite converted, and then purified using a workflow developed by Epigenomics. Detection of DNA is accomplished via a novel duplex real-time PCR assay combining a highly sensitive DNA methylation specific mSEPT9 DNA detection assay and AGT3 DNA measurement as an internal control. The entire workflow has been optimized to increase robustness and improve the ease-of-use in the laboratory routine.

Results: A just completed case-control study with 103 CRC cases and 134 colonoscopy negative controls, demonstrated that the new duplex assay detected about 70% of the CRCs with about 90% specificity in the colonoscopy negative group. Performance for early, localized disease was remarkably high and confirmed the utility of the test.

Figure 1.

P.03 INITIAL OUTCOME DATA FROM SCOTTISH BOWEL SCREENING PROGRAMME

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Objectives: Three pilot rounds of screening demonstrated the effectiveness of asymptomatic population screening for colorectal cancer in Scotland. Based on these results, a national Programme started to roll out to all 14 Scottish NHS Boards in June 2007. The initial data for the Programme have now been published. This is the first report to analyse the impact of Incident and Prevalent NHS Boards on the overall Programme indicators.

Method: The results of the Scottish Bowel Screening Programme (SBSP) were recently released for the period June 2007 to May 2009. These data can now be compared to the data collected in the three pilot rounds conducted in Scotland. With the Programme there are three Incident Boards in which the pilot rounds were done, these are now in the fourth screening round. There are also 11 Prevalent Boards in which the population has not been screened before. The Programme evidence-based changes have been introduced to optimise outcomes. The Programme progressed to using a two-tier reflex strategy that includes a qualitative FIT second test following an equivocal initial gFOBT. The results here compare outcomes over time.

Results: The data from the Key Performance Indicators (KPI) are of particular interest. These are uptake of screening and correct response to first kit. The pilot round data were 55.0%, 53.0% and 55.5% and 43.8%, 51.5% and 53.7% respectively. The Incident Boards continue to increase to 56.8% and 54.9% in the Programme; the Prevalent Board’s uptakes are lower than the first pilot round [53.8%], response to first kit is also low [51.5%]. Colonoscopy uptake has decreased over the three pilot rounds 85.3% to 81.3%. The Incident Boards continue this trend, 71.9% in the Prevalent Boards is slightly higher than the Programme overall 79.1%, but not at the high first round result. The neoplasia detection rate and stage at presentation data show that Prevalent Boards had more cancer detected than the Incident Boards and that, in Prevalent Boards, more cancers were detected at an early stage. The Programme positive predictive value (PPV) for total neoplasia, 43.0%, has slightly increased from third round value 36.6%. The PPV in the Incident Boards is 37.4% and 48.5%, in the Prevalent Boards, reflecting the first pilot round results. The variation in PPV could be a reflection of the pilot rounds using a gFOBT-based algorithm. The SBSP uses a qualitative Faecal Immunochemical Test (FIT) second test when with the initial gFOBT gives a weak positive result. The results here compare outcomes over time.

Conclusion: These data demonstrate the ongoing efficacy of the SBSP. The break down into Incident Boards demonstrates the ‘steady state’ in a population in their screening fourth round. The outcomes in the Prevalent Boards show greater comparability with the outcomes of the first pilot screening round. The data also show the outcomes with the two-tier reflex gFOBT/FIT strategy.
P.04 PREVALENCE AND INCIDENCE SCREENING IN A POPULATION-BASED FOBT COLORECTAL SCREENING PROGRAMME

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Introduction: Between March 2000 and May 2007 three rounds of biennial guaiac FOB testing were conducted in North-East Scotland for all individuals aged 50-69. As this was an ongoing, dynamic programme, the second and third rounds consisted of a combination of prevalent and incident screening episodes, and this study was performed to examine the effect of prevalence and incidence screening, irrespective of round.

Results: Of the total number of screening episodes in all three rounds (510,990), 248,998 (48.5%) were prevalence, 163,483 (32.0%) were first incidence, and 98,509 (19.3%) were second incidence. Of those undergoing prevalence screening, 169,508 (68.1%) were prevalent in the first round; 38,283 (15.4%) were prevalent in the second round, and 4,1207 (16.5%) were prevalent in the third round. Uptake of 1st invites prevalence screening was 52.9% and was similar in all three rounds, but uptake of 2nd and 3rd prevalence screening was 44.8 and 11.8% respectively. In the cohort invited in the first round, uptake of prevalence screening rose from 52.9% in the year 1995-96 to 61.9% in the year 2004-05. The uptake of colorectal cancer screening was 86.8%. These figures were 1.7% and 90.4% for the first incidence screen, and 1.1% and 94.5% for the second incidence screen. The PPV of a positive FOBT for cancer in prevalent screening was 11.8%, for the first incidence screen it was 6.5% and for the second incidence screen it was 7.6%. The figures for the PPV for adenoma were 35.5%, 29.4% and 26.7% respectively.

Conclusion: These data demonstrate that repeated invitations to those who refuse screening does increase the number of individuals who take up the offer, both for prevalence and incidence screening. Although the PPVs for both cancer and adenomas fell between the prevalent screening and the first incidence screen, they did not fall between the first and second incidence screens. The deterioration in cancer stage from prevalence to incidence screening suggests that some cancers picked up at incidence screening may have been missed on prevalent screening, but the stage distribution is still favourable. These are the first data from an ongoing population colorectal screening programme to vindicate the policies of continuing to offer screening to defaults, and continuing to offer biennial screening to those who have accepted previous offers.

P.05 CLINICAL AND PATHOLOGICAL FACTORS RELATED WITH YEARS OF POTENTIAL LIFE LOST BY COLORECTAL CANCER

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Objectives: Colorectal cancer (CRC) is one of the most frequently diagnosed tumors worldwide. This disease affects all age-groups including younger members of the population. A widely used indicator of premature death is the Years of Potential Life Lost (YPLL). The objective of this study was to analyze YPLL due to CRC in our population. We performed a descriptive cross-sectional study of 980 consecutive patients diagnosed and treated at the General Surgery Department of a University Hospital between the years 1995 and 2002 inclusive. The endpoint of the study was to calculate individual "years of potential life lost" (YPLL). A data analysis to compare each independent variables (age, sex, symptoms, type of surgery, etc.) with the variable YPLL was performed.

Results: Of 980 patients, the final study sample was 794 patients; 413 (52%) men and 381 (48%) women. Mean age was 65.3 years. The most frequent initial symptom was rectal bleeding (339 patients, 42.7%). In 698 patients (89.3%) surgery was elective and in 84 (10.7%) it was emergency surgery. Of 84 emergency interventions, 56 patients (6.4%) died. The number of deaths increased with age, sex, and presence of rectal bleeding as initial symptom. The most frequent causes of death were postoperative complications were recorded in 235 patients (29.6%), and perioperative mortality in 13 (1.7%) patients. Chemotherapy with or without postoperative radiotherapy was administered to 421 (53%). At the end of the study period, 351 (44.2%) patients had died of CRC. The mean global YPLL for the 351 patients who died of CRC was 15.18 years (SD:10.69; CI95%: 14.05-16.30). Statistically significant association with YPLL was found for the following variables: age (p<0.001), sex (p=0.002), presence of colorectal cancer as initial symptom (p=0.01), curative surgery (p<0.001), emergency surgery (p<0.01), rectum cancer localization (p=0.003), TNM stage (p<0.001) and the administration of chemotherapy and/or adjuvant radiotherapy.

Conclusion: The highest values of YPLL due to CRC are found in young male rectum cancer patients, patients with colorectal cancer as initial symptom, and undergoing non-curative emergency surgery and receive postoperative adjuvant chemotherapy and/or radiotherapy, whose TNM stage have been more advanced at diagnosis. Age, sex, TNM stage and rectum localization of the tumor are independent prognostic factors for YPLL.

P.06 CLINICAL SIGNIFICANCE OF FECAL OCCULT BLOOD AND FECAL CEA DUAL RAPID TEST KIT FOR THE DETECTION OF COLORECTAL CANCER

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Introduction: Fecal occult blood test (FOBT) which is used as a screening tool for colorectal cancer has a limited clinical application due to low sensitivity, and colonoscopy, though it is highly accurate, it has associated with complications, high cost and requirement of specialist. So the role of colonoscopy as a tool for colorectal cancer screening test is under investigated. Herein authors made a dual kit for fecal occult blood and CEA testing, and studied its efficacy as a screening tool for colorectal cancer.

Method and materials: CEA/FOBT dual test kit is composed of using anti-CEA and anti-Hgb. Anti-CEA antibody concentration is targeted for the serum CEA level of 50ng/ml and is detected as a band from. From March 2007 to September 2008, we collected stools preoperatively from colorectal cancer patients expected elective operation. And we tested stools with CEA/FOBT dual test kit and compared its result with other clinical factors such as age, gender, familial history, cancer location and pathological factors. This study is approved by IIR of our institution and informed consents were obtained from patients before conducting studies.

Results: Among 143 patients, FOBT is positive in 86 cases out of 143 (60.4%) and CEA is positive in 92 cases out of 143 (64.3%). Among 57 FOBT negative patients, 23 cases are revealed as CEA positive. So the CEA/FOBT dual test kit has sensitivity of 76.2% (109/143) of colorectal cancer. FOBT and fecal CEA has significant correlation (p-value<0.001). FOBT has significant correlation with serum CEA level >5, T-stage, neural invasion, M-stage and lymphatic invasion. And fecal CEA is correlated with multiple cancer of colon and T-stage.

Conclusion: If we add fecal CEA test to FOBT, then we can detect 16.1% patients with colorectal cancer additionally. In total, herein, we can detect preoperatively 76.2% colorectal cancer patients and it has it's effectiveness.

P.07 TEA POLYPHENOL MAY INHIBIT MICROSATELLITE INSTABILITY COLORECTAL CANCER BY DOWN REGULATING THE EXPRESSION OF HES1, JAG1, MT2A AND MAFa

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Introduction: Tea polyphenol has been shown to have anti-colorectal cancer and anti-genesis mutation effects, although the mechanism of inhibition of MSI colorectal cancer is not known. Using LoVo cells and SW480 cells treated with an aqueous solution of tea polyphenol, cell proliferation was detected by the MTT method, changes in microsatellite sequences by the Genescan method and changes in the gene expression of LoVo cells using Illumina expression arrays. The proliferation inhibition rate of LoVo and SW 480 cells treated with tea polyphenol increased with increasing drug concentration and showed an increasing tendency with time. The proliferation inhibition rate of LoVo cells with tea polyphenols was higher than that of SW480 cells, and there was a significant difference in the proliferation inhibition rate at 24h, 72h and one week. The microsatellite sequence of LoVo cells treated with...
P.08 COMPARISON OF RESULTS OF VIRTUAL COLON DISSECTION TOOLS USED IN CT COLONOGRAPHY WITH RESULTS OF CONVENTIONAL ENDOSCOPIC VIEW IN DETECTIONS OF SMALL POLIPS, GOLD STANDARD WAS A CONVENTIONAL COLONOSCOPY

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Objectives: The aim of this study was to determine the capability and accuracy of virtual colon dissection tool to detect small colonic polyps in CT colonography.

Method: CT colonography was performed in 500 patients. 320 patients were asymptomatic. 180 patients had an abdominal complaint, or occult gastrointestinal bleeding. All patients had a conventional colonoscopy after virtual colonoscopy between 1-3 days. All patients were scanned using 16 detector row helical CT scan. An experienced reader evaluated the data on a dedicated CT workstation. With virtual colon dissection tool the entire inner surface of the colon can be studied at a glance without the need for navigation.

Results: Conventional colonoscopy revealed 362 colonic lesions in 50 patients. 236 lesions were smaller than 5 mm, 51 lesions were 5-10 mm and 75 were 10 mm or larger. The colon dissection mode had an overall per-lesion sensitivity of 55.6%, for lesions smaller than 5 mm, 76.7% (5-10 mm) and 81% for lesions larger than 10 mm. The endoluminal view mode had an overall per-lesion sensitivity of 56% (< 5 mm), 74% (5-10 mm), and 95% for lesions larger than 10 mm. The average time consumption for evaluation with the colon dissection mode was 14 min vs. 32 min with the endoluminal view mode.

Conclusion: The colon dissection mode provides a significant time advantage during evaluation of CT colonography data sets. With colon dissection mode high sensitivity can be achieved. It is especially superior in detecting lesions smaller than 5 mm.

P.09 THE UTILITY OF MDCT PERFUSION EXAMINATION IN DETECTION OF METASTATIC LYMPH NODES OF RECTAL CANCER

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Objectives: Assessment of the role of computed tomography perfusion (CTP) study for the differentiation between malignant and benign enlarged perirectal, pelvical, and retroperitoneal lymph nodes. 

Method: A prospective study was conducted on a 31 consecutive patients (17 M, 14 F aged 48-72) with a histologically proven rectal cancer. The perfusion study was done after contrast-enhanced conventional abdominal MDCT study. A dynamic acquisition (8x3 mm slices) was performed and the perfusion values were calculated using a modified deconvolution-based analysis, with the application of CT perfusion software. Region of interest placed over the biggest lymph node was found in a previous a modified deconvolution-based analysis, with the application of CT perfusion (8x3 mm slices) was performed and the perfusion values were calculated using a modified deconvolution-based analysis, with the application of CT perfusion software. Region of interest placed over the biggest lymph node was found in a previous CT study. Postprocessing-generated maps showed perfusion (P), peak enhancement intensity (PEI), time to peak (TTP), blood flow (BF), blood volume ml/100ml (BV). Data were statistically analyzed with Wilcoxon sign test and results compared with histopathohal findings.

Results: On the perfusion maps, metastatic nodes showed hyperperfusion compared to benign ones. The mean value of BV was 2.9 (+0.29) and TTP was 25 sec (+4.2 sec). Compared to non-malignant nodes, the malignant ones showed significantly lower BF and BV values (p<0.009). The accuracy of detecting malignant nodes was 89%, sensitivity 91%, specificity 83%, positive predictive value 90.5%, and negative predictive value 76.7%.

Conclusion: CTP can be a good tool in distinguishing benign and malignant lymph nodes in rectal cancer and might be useful in re-staging.

P.11 WHOLE BODY DIFFUSION WEIGHTED IMAGING FOR DISTANT STAGING IN COLORECTAL CANCER - FEASIBILITY AND FUTURE CHALLENGES

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Objectives: Patients with colorectal cancer are screened for distant metastases to evaluate their prognosis and determine the appropriate treatment plan. To perform a complete distant staging, multiple examinations, consisting of liver and/or chest CT, chest X-ray, liver ultrasound or PET-CT are generally required. CT and PET-CT are the most well known one-stop-shop techniques for whole body screening, but require a relatively high dose of ionising radiation. Whole body diffusion weighted MRI (WB-DWI) is a new concept, that might prove to be a promising alternative. Diffusion MRI derives its contrast directly from differences in tissue cellularity and has been reported to be promising for the discrimination between tumoural and non-tumoural structures throughout the body. WB-DWI renders PET-like images, but does not require the use of ionising radiation or exogenous contrast agents. The purpose of this study was to evaluate the feasibility of WB-DWI for (local) and distant staging in rectal cancer and compare the lesion detectability with conventional distant staging techniques (CT and/or PET-CT).

Method: 6 volunteers and 9 rectal cancer patients with known distant metastases underwent WB-DWI (DWIBS-method (Tahara et al, 2004), -values, 0.800 s/mm², scan time 16 minutes). Five patients were scanned at primary staging, 2 after chemoradiation (CRT) and 2 both pre- and post-CRT. 3D maximum intensity reconstructions in inverted greyscale were generated for image evaluation. Two readers analysed all images (in consensus) for suspected lesions. Histogram was the standard reference for the primary tumours. CT (n=5), PET-CT (n=4) and histology (n=4) were the reference for distant metastases.

Results: Image quality was good in all 15 subjects. All rectal tumours could be visualised on WB-DWI. On PET-CT, the 9 patients had a total of 62 distant metastases (43 liver metastases, 19 distant lymph-node metastases), of which 13 were histologically confirmed. 53/62 lesions (85%) could be identified with WB-DWI. In two patients after chemotherapy, residual liver lesions (3-17 mm) that were still visible on CT and histologically confirmed after liver surgery could not be identified on DWI. In all volunteers and patients, pronounced axillary and inguinal lymph nodes were visible on WB-DWI. These nodes visually resembled the metastatic nodes along the abdominal and inguinal vessels as seen in patients and could harbour a risk for false positives.

Conclusions: WB-DWI images of adequate quality can be obtained within an acceptable time frame. Lesion detection is promising, but with a risk for false positives. After chemotherapy, WB-DWI seems to have limitations in detection of residual lesions. Though several challenges need to be addressed, whole body diffusion weighted MR imaging may potentially become a promising alternative for whole body staging in colorectal cancer.
P.12 ACCURACY OF GADOFOSVESET-ENHANCED MRI FOR PREDICTING NODAL STATUS IN PRIMARY RECTAL CANCER

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Objectives: Evaluation of nodal status in rectal cancer is essential to stratify patients for differentiated treatments based on their individual risk for local recurrence. None of the modern imaging techniques used for rectal cancer staging (CT, MRI and endorectal ultrasound) are, however, accurate enough to discriminate between benign and metastatic nodes. These techniques mainly rely on size as a criterion, even though size is known to be a very unreliable predictor for rectal cancer nodes. Apparently the anatomical information from standard techniques is insufficient and additional functional information is required. Gadofosveset is a new MR contrast agent, traditionally used for MR angiography. Recently, Gadofosveset-enhanced MRI was also shown to be feasible for discrimination of metastatic lymph nodes in rectal cancer. This study aims to validate the accuracy of MRI with Gadofosveset for nodal staging in patients with primary rectal cancer.

Method: 58 patients underwent preoperative MRI including standard T2-weighted and additional Gadofosveset-enhanced 3D T1-weighted sequences. 23 patients underwent total mesorectal excision (TME) with (n=18) or without (n=5) 5x5 Gy radiation and 35 locally-advanced patients underwent TME with neoadjuvant chemoradiation (n=20). The latter underwent a restaging-MRI 6-8 weeks after chemoradiation, which was used for validation with histology. An MR-rectum expert (reader 1) and abdominal radiologist (reader 2) predicted each node for benign or malignant; first on T2W-MRI, then after addition of Gadofosveset-MRI using a confidence level (0=definitely benign to 4=definitely malignant). Each node was drawn on an anatomical template to ensure lesion-by-lesion matching with histology. ROC-curves were evaluated and corresponding sensitivity/specificity figures were calculated. Kappa-statistics were performed for interobserver-agreement.

Results: In 58 patients, 458 nodes were analysed, of which 68 N+ in 23 patients. On a lesion-by-lesion basis, the area under the ROC-curve (AUC) for reader 1 improved from 0.83 for T2W-MRI to 0.96 when Gadofosveset-MRI was added (p<0.0001). For reader 2, the AUC improved from 0.85 to 0.90 (not significant). Corresponding sensitivity, specificity, PPV and NPV for Gadofosveset-enhanced MRI were 83%, 97%, 83% & 97% for reader 1 and 63%, 93%, 60% & 94% for reader 2. On a per patient basis the AUCs improved from 0.74 (reader 1) and 0.79 (reader 2) for T2W-MRI to 0.89 and 0.85 for Gadofosveset MRI. Interobserver agreement was good both for T2W and Gadofosveset-MRI (k=0.72 and 0.68).

Conclusions: Gadofosveset-MRI is highly accurate for prediction of nodal status in the hands of an experienced reader. ypN0-patients can be selected with high NPV, regardless of the reader’s experience. Addition of Gadofosveset could increase accuracy for nodal staging to a level sufficient for safe clinical decision making.

Figure 1. ROC-results for T2W-MRI and Gadofosveset

Figure 2. Patient with massive nodal mets on WB-DWI and PET
P.14 MR FOR RECTAL CANCER AT 1.5 TESLA IS SUFFICIENT FOR T STAGING; 3.0 TESLA MRI DOES NOT NECESSARILY IMPROVE A RADIOLOGIST’S PERFORMANCE

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Objectives: Standard surgical treatment for rectal cancer consists of total mesorectal excision (TME). Small tumours that are confined to the bowel wall (T1-2) could undergo local excision as a less invasive alternative to TME, but only when the preoperative identification of T1-2 tumours is accurate enough and there is no - or very limited - risk for undertreatment. We know from literature that standard MRI is moderately accurate for selection of T1-2 tumours. The main problem is that standard MRI (generally performed at 1.5 Tesla) is not able to discriminate between tumour stranding into the perirectal fat (T3) and normal desmoplastic reaction (T1-2) and many T1-2 tumours are overstaged. In theory, MRI at 3.0 Tesla could improve the accuracy for discrimination between T1-2 and T3 tumours, as the higher signal to noise ratio at 3.0 Tesla allows for images with improved contrast and higher image resolution. Therefore, the purpose of this study was to evaluate the diagnostic performance at 3.0T-MRI for selecting T1-2 tumours for radiologists with different levels of expertise, compared to 1.5T-MRI.

Materials and method: 13 patients underwent standard T2-weighted MRI (sagittal, axial and coronal) at both 3.0T and 1.5T followed by surgery. Two expert MR-rectum readers and 2 experienced radiologists without specific MR-rectum expertise predicted the T-stage on 1.5T and 3.0T MRI subsequently, blinded for each others and histological results. Likelihood of tumour confined to the bowel wall was scored using a confidence-level score (0=definitely outgrowing wall to 4=definitely confined to the wall). ROC-analyses were performed to compare 1.5T to 3.0T-MRI. Corresponding positive predictive value (PPV) and negative predictive values (NPV) were calculated.

Results: At histology, 7/13 patients had a T1-2 tumour. Mean PPV, NPV and area under the ROC-curve (AUC) for the expert-readers were 78%, 60% and 0.786 at 1.5T compared to 66%, 53% and 0.714 at 3.0T. This difference was not significant (p>0.05). Mean PPV, NPV and AUC for the non-expert readers were 78%, 72% and 0.733 at 1.5T versus 77%, 67% and 0.715 at 3.0T. This difference was not significant (p>0.05). Interobserver agreement for the expert readers was 0.54 at 1.5T versus 0.31 at 3.0T. For the non-experts, the interobserver agreement was 0.43 at 1.5T versus 0.16 at 3.0T.

Conclusions: MRI at 1.5T is sufficient for predicting tumours confined to the bowel wall with sufficient PPV, regardless of the readers’ experience. MRI at 3.0T does not improve performance for prediction of T1-2 tumours as compared to MRI at 1.5T, regardless of the reader’s experience. Interobserver agreement is better at 1.5T. Despite of the theoretrical advantages of 3.0 Tesla MRI, it does not improve accuracy for selection of patients for local excision. MRI at 1.5 Tesla remains the standard.

P.16 METHYLENE BLUE ASSISTED LYMPH NODE DISSECTION ENSURES AN ADEQUATE LYMPH NODE HARVEST IN NEOADJUVANTLY TREATED COLORECTAL CANCER

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Objectives: Exact lymph node staging is essential for prognosis estimation and treatment stratification in colorectal cancer. A minimal number of 12 investigated lymph nodes (LN) is recommended by the UICC. Especially in neoadjuvantly treated patients this number is reached in practice only in minority of cases. We recently introduced methylene blue assisted lymph node dissection (MB-LND) as a highly effective method to improve lymph node harvest in gastrointestinal cancers. Now, we analysed our data concerning its effect in cases with neoadjuvant therapy.

Method: MB-LND was performed in 53 rectal and 1 colon cancer cases (methylene group). For that fresh specimens were brought immediately after the resection to the pathology Department After identifying the inferior mesenteric artery 20 ml of methylene blue solution was injected. LN dissection was carried out after formalin fixing over night. A historical group of 47 rectal cancer cases were conventional lymph node dissection was performed served as control.

Results: The injection was easy and successful performed in all cases of the methylene group. The detection was facilitated by the light blue staining of the LN (Figure 1). The lymph node harvest was highly significantly improved in the methylene group compared to conventional dissection with mean LN numbers of 29 ± 11 and 10 ± 4 (P < 0.001), respectively (Figure 2). Insufficient LN harvest occurred in 68 % of the control group cases and in no case of the Methylene group. Node positivity was found in 13 cases of each group. However, there was a non significant trend of more metastasized LNs (38 vs. 41) and a higher proportion of N2 cases in the methylene group (7 vs. 4).

Conclusion: MB-LND is a highly effective method to improve LN harvest in neoadjuvantly treated colorectal cancer and guarantees a sufficient harvest in adequate resected specimens. Furthermore our data show that LNs do not vanish after neoadjuvant therapy. The reported poor harvest results are obviously caused by a reduced detectability.
P.17 RECTAL CANCER VEGFR & FDG-PET/CT CORRELATIONS IN MOLECULAR STAGING AND RESTAGING (POSTNEOADJUVANT)

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Purpose: Molecular expression and bio-imaging offers relevant information to guide neoadjuvant treatment and interpret chemohoradiation response.

Method & materials: From 11/2005 to 06/2008 41 prospectively resected patients (cT3 88%, cN+ 89%) were studied with FDG-PET/CT imaging (SUV_{max} and multidimensionality information) at initial staging and postneoadjuvant/preoperative restaging. Neoadjuvant treatment contained Oxaplatin, oral fluopirimidines and 50.4 Gy pelvic irradiation. VEGFR was determined by immunohistochemistry in the diagnostic biopsy specimen and post-chemoradiation residual cancer. Values and observations were correlated with pathological downstaging/response effects (TRG scale).

Results: VEGFR expressed in 31/32 biopsies (100%=28). Postneoadjuvant expression was 24/32 (100%=13). Intensity of expression was maximal in 19/32 in pre and 0/32 in post cancer tissue. FDG-PET/CT mean volumetry of the staging rectal lesion was 49.66 mm³ (+/- 10.62) and restaging of 7.34 mm³ (+/- 1.63). SUV_{max} pre ranged from 3.7 to 17.10 (mean 8.77) and post-neoadjuvant ranged from 0 to 7.29 (mean 2.64). (p<0.001)

pT downstaging (categories pT0-2) correlated with SUV_{max} at restaging (1.66 +/- 1.14 vs 3.61 +/- 2.02, p < 0.008) and volumetry (3.96 +/- 2.67 vs 11.25 +/- 12.35, p=0.002). TRG scale categories 3/4 (responders) confirmed both findings: elevated restaging SUV_{max} (p=0.04) and large volumetry (p=0.01). VEGFR at restaging correlated expression intensity stabilization with high SUV (3.07 +/- 2.04 vs 1.44 +/- 0.79, p=0.004) and superior volumetric (15.13 +/- 14.85 vs 2.77 +/- 2.45, p=0.0001) values, also at restaging.

Conclusion: Rectal cancer is a valid model to study molecular staging correlations. Pathological resistant disease to chemoradiation shows a significant association with unfavourable molecular restaging observations: VEGFR stabilization expression, elevated SUV max and increased residual volumetry.

Supported by a grant of Bio-medical Foundation of MMA.

P.18 PATENT BLUE STAINING AS A METHOD TO IMPROVE LYMPH NODE DETECTION IN RECTAL CANCER FOLLOWING NEOADJUVANT TREATMENT

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Objectives: Lymph node involvement is an important prognostic factor in rectal cancer. A low number of lymph nodes is associated with worse outcome in patients with any N-stage. The international AJCC guidelines for rectal cancer recommend a minimum of twelve evaluated lymph nodes in order to score a valid nodular classification. The objective of this study was to evaluate the effect of patent blue staining of surgical specimens on the number of harvested lymph nodes at pathological evaluation.

Method: Consecutive patients with rectal cancer, who were registered in a prospective database from March 2007 to September 2009, were evaluated. All patients underwent either low-anterior resection or abdomino-perineal resection for rectal cancer by means of total mesorectal excision after neoadjuvant treatment. In the first period specimens were never stained. Later, patent blue staining was introduced. This was injected directly after resection by the operating surgeon, either in the mesorectum or into the inferior mesenteric artery. Pathologic evaluation of the specimen and harvesting of the lymph nodes were performed by various pathologists.

Results: A total number of 234 patients (155 male and 79 female) underwent total mesorectal excision in the study period. Eighty-nine specimens were not stained with patent blue (NB), 82 specimens were stained with patent blue in the mesorectum (MB) and 63 were stained with patent blue in the inferior mesenteric artery (AB). The mean number of lymph nodes harvested was 6.4 in the non-stained group, 11.5 in the mesorectal stained group and 17.0 in the inferior mesenteric artery group which is a highly significant difference (p < .0001, figure 1). The percentage of patients who met the AJCC criterion of a minimum of twelve lymph nodes increased significantly from 11.2 (NB) to 68.3 (AB). Patient characteristics such as age, sex, preoperative tumour stage, type of neoadjuvant treatment and type of surgical procedure did not differ between these groups (table 1). All patients received neoadjuvant radiotherapy (46 or 72 percent received long scheme radiotherapy), with or without chemotherapy.

Conclusion: This is the first report that shows promising results of this relatively simple technique. The use of patent blue improves the detection of lymph nodes in total mesorectal excision specimens, especially when injected in the inferior mesenteric artery. This also applies for patients who underwent long scheme neoadjuvant treatment.

**Table 1. Data table**

<table>
<thead>
<tr>
<th>Patent blue staining</th>
<th>None (n = 89)</th>
<th>Mesorectum (n = 82)</th>
<th>IMA (n = 63)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>61</td>
<td>57</td>
<td>37</td>
<td>334</td>
</tr>
<tr>
<td>Age ± SD</td>
<td>65.3 ± 11.2</td>
<td>64.3 ± 9.8</td>
<td>65.4 ± 12.1</td>
<td>768</td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Long scheme radiotherapy</td>
<td>70</td>
<td>53</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>26</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LA</td>
<td>38</td>
<td>47</td>
<td>36</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>35</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Tumor stage*</td>
<td></td>
<td></td>
<td></td>
<td>0.088</td>
</tr>
<tr>
<td>- T1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>- T2</td>
<td>38</td>
<td>32</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>39</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Mean lymph nodes harvested (95% CI)</td>
<td>6.4 (5.3 - 7.5)</td>
<td>11.5 (9.9 - 13.1)</td>
<td>17.0 (14.7 - 19.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AJCC criterion met, 12 or more lymph nodes (%)</td>
<td>10 (11.2)</td>
<td>37 (45.1)</td>
<td>43 (68.3)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* Two unknown because MRI-scan could not be conducted (pacemaker)
P.19 VARIATION IN LYMPH NODE EVALUATION IN RECTAL CANCER: A NATIONWIDE POPULATION-BASED STUDY IN THE NETHERLANDS

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Objectives: The stage of disease is an important prognostic factor in rectal cancer. For successful preoperative staging and subsequently an accurate estimation of prognosis, a sufficient number of lymph nodes has to be examined. The aims of this study were: 1) to describe the variation in lymph node examination in patients with rectal cancer in the Netherlands; 2) to identify factors associated with adequate lymph node evaluation and 3) to analyse the relation between the number of evaluated lymph nodes and survival.

Method: Data from all patients with rectal carcinoma stage I-III who underwent surgical treatment, diagnosed in the period 2000-2006 were retrieved from the Netherlands Cancer Registry. Multilevel logistic analysis was performed to examine the influence of relevant factors on the number of evaluated lymph nodes. Cox regression analysis was used to analyse the association between the number of examined lymph nodes and survival.

Results: The number of examined lymph nodes was determined for 11,417 (92%) of the 12,447 tumours. The median number of evaluated lymph nodes was 7, ranging from 4 to 11 between pathology laboratories. The increasing number of evaluated lymph nodes was associated with an increased proportion of patients with positive lymph nodes. Males, younger patients, tumours with a larger Department of invasion, tumours with nodal involvement, patients who received postoperative radiotherapy or no radiotherapy, patients who underwent a low anterior resection and patients whose lymph nodes were evaluated in an academic pathology laboratory were less likely to have 9 or less lymph nodes evaluated. After adding these factors to the model, an unexplained variation between the pathology laboratories and the hospitals remained. Both among patients with positive nodes as among patients with negative nodes, the risk of death decreased with increasing number of evaluated lymph nodes.

Conclusion: There was a large variation in lymph node evaluation with diversity between types of hospitals and pathology laboratories in patients with rectal cancer in the Netherlands. Adequate lymph node evaluation was associated with survival. Improvements in lymph node evaluation by hospitals and pathology laboratories could improve staging, leading to more reliable estimation of prognosis.

P.20 IMPROVED SELECTION OF PATIENTS FOR HEPATIC SURGERY OF COLORECTAL LIVER METASTASES WITH FDG-PET: RESULTS OF THE RANDOMIZED DUTCH POLE STUDY

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Objectives: Careful selection of patients who may benefit from surgical treatment of colorectal liver metastases is critical. Staging by PET with FDG is thought to be better than conventional staging. Evidence that the addition of FDG-PET leads to superior clinical results and improved clinical management in these patients are lacking. In this randomised controlled trial, we investigated whether the addition of FDG-PET is beneficial and reduces the number of futile laparotomies.

Method: 150 patients with colorectal liver metastases selected for surgical treatment by imaging with CT scan were randomly assigned to CT imaging only (n=75) or CT imaging plus FDG-PET (n=75). Primary outcome measure was futile laparotomy, defined as any laparotomy that did not result in complete tumour treatment, that revealed benign disease or that did not result in a disease free survival period longer than 6 months.

Results: Clinical characteristics were similar for both groups. The number of futile laparotomies was 34 (45%) in the group without PET and 21 (28%) in the group with PET, the relative risk reduction was 38% (95%CI = 4%-60%).

Conclusion: Addition of FDG-PET to the work-up for surgical resection of colorectal liver metastases prevents unnecessary surgery in one out of six patients.

Research support: Supported by ZonMW (DO 2001 #945-10-017)

P.21 PATHOLOGICAL WORK-UP AFTER NEOADJUVANT TREATMENT IN RECTAL CARCINOMA: AN INTERLABORATORY TEST MEASURING INTEROBSERVER AGREEMENT IN ASSESSING TUMOR REGRESSION GRADE

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Objectives: Neoadjuvant therapy is considered standard practice for locally advanced rectal cancer. Preoperative radiochemotherapy induces histological changes of various degrees and forms in tumor tissues. Several tumor regression grading systems have been proposed for use in histopathological evaluation of tumor response.

Method: For the interlaboratory test, slides representing the tumor area of ten rectal carcinomas treated with neoadjuvant radiochemotherapy have been selected from the archives of the Institutes of Pathology of Leipzig and Erlangen and submitted to seven Institutes of Pathology throughout Germany. Tumor regression grade for each tumor was assessed independently by seventeen participating pathologists according to six different grading systems. Five of these grading systems are common practice, whereas the sixth one has just recently been created during a pathologists’ meeting. The degree of interobserver agreement was calculated using Kappa statistics.

Results: The overall k scores range from 0.52 to 0.63 for the six grading systems corresponding to a moderate to good agreement. A newly created system came up with the best k score. Regarding single categories, the extreme of the spectrum in terms of complete regression delivers the highest k score and causes least controversy.

Conclusion: So far, there is no standard system to assess tumor regression grade after neoadjuvant therapy of rectal carcinoma. However, this is essential, as pathological evaluation of tumor regression serves as a basis to further investigate the correlation between response and prognosis. Based on the results and the insights gained during the interlaboratory test, further efforts will be necessary to create a reliable standardized grading system.

P.22 IMPROVABLE QUALITY OF DIAGNOSTIC ASSESSMENT OF COLORECTAL CANCER IN SOUTHERN NETHERLANDS

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Objective: To determine the extent of guideline implementation of the diagnostic approach to patients with colorectal cancer (CRC) in southern The Netherlands in 2005, with special focus on colonoscopy.

Method: Data were gathered from the medical records for a random sample of 257 colon and 251 rectal cancer patients newly diagnosed in 2005 and recorded from the Eindhoven Cancer Registry. Adherence to guidelines was determined for diagnostic assessment. Multivariable logistic regression analysis was conducted to assess determinants of complete colonoscopy.

Results: Diagnostic assessment was carried out mainly by internists (50%) and gastroenterologists (36%). Colonoscopy was performed in 83% of patients with proximal/transverse colon cancer, 55% of those with distal colon cancer, and 65% of those with rectal cancer. A tumour biopsy was taken of 84% of colon and 93% of rectal tumours. Colonoscopy completeness was lower for patients with co-morbidity, obstructing tumours, and patients with poor bowel preparation. Abdominal ultrasound was performed for 72% of colon and 52% of rectal cancer patients and a thoracic X-ray of over 80% of CRC patients. Computed tomography (CT) of the abdomen was done in over half of the colon cancer cases and a pelvic CT scan or magnetic resonance imaging (MRI) in 36% of rectal cancer cases.

Conclusion: Improvements in adherence to diagnostic guidelines for CRC appear possible, especially in the performance of imaging procedures. Among patients where complete visualisation of the colon was not feasible with colonoscopy, imaging techniques such as virtual CT might be of added value in the near future.
Method: Data of all patients with curative colon cancer (pTany Nany M0) diagnosed in 1999-2007 whose resection specimens were evaluated by the Institute for Pathology and Medical Microbiology in Eindhoven, (n=1,501) were included. Feedback to specialists, increased fixation time, and ex-vivo injection of the specimen with Patent blue V dye were used to increase LN detection rate. Trends in the proportion of patients with insufficient LNs examined were investigated; moreover, the Patent blue stained patients (n=86) were compared with a group of unstained patients (n=84). Based on the decrease in the proportion of high-risk node-negative patients, a calculation of chemotherapy-related costs saved was made.

Results: The proportion of patients with <12 LNs examined decreased from 87% in 1999 to 48% in 2007 (p trend<0.0001). In the stained group this was 37%, versus 56% for the unstained group (p=0.010). In 1999, 79% of stage II patients were high-risk compared to 55% in 2007, which translates to a saving of almost 1,000,000 euro based on the decrease in the proportion of high-risk node-negative patients who would otherwise have received adjuvant chemotherapy.

Conclusion: A diverse set of measures increased the number of examined lymph nodes among patients with colon cancer. Large savings can be made due to the reduced proportion of high-risk node-negative patients who would otherwise have received adjuvant chemotherapy.

Figure 1. Patients with sufficient lymph nodes examined.

Figure 2. Number of lymph nodes harvested.
**P.26** IS RECTAL CARCINOMA A CHRONIC DISEASE? LONG-TERM FOLLOW-UP AND QUALITY OF LIFE EVALUATION

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**Objectives:** A cohort study was performed to investigate oncological outcome, late adverse effects and quality of life (QoL) in rectal carcinoma patients with long-term follow-up (median 8.8 years).

**Method:** The prospectively collected data of 268 consecutive patients with rectal carcinoma, treated between 1995 and 1997 at the Department of Surgery, University Hospital Erlangen, Germany, was analyzed. Late adverse effects were defined as the need for hospital admission more than 6 months after primary tumor resection. In 97 long-term survivors (median 13 years) QoL was evaluated by the EORTC questionnaires QLQ-C30 and QLQ-CR38.

**Results:** 10-year overall survival was 48.1%. 41 patients (15.3%) were treated in palliative intention, 8 patients (3.0%) died postoperatively. Out of 219 patients with curative resection 67 patients (30.6%) suffered from recurrent disease (locoregional or distant), in seven patients (10%) late first recurrence with diagnosis more than five years after start of primary treatment was observed. In 13 patients second malignancies occurred. 70 out of 219 curatively resected patients (32.0%) either had a permanent stoma or a late adverse effect (fistula n=5, anorectal dysfunction n=14, small bowel obstruction n=18, abdominal hernias n=6, ureteric stricture n=4). Anorectal dysfunction and small bowel obstruction were observed significantly more frequently in patients with primary multimodal treatment (p<0.001 and p=0.049). Comparing QoL in 97 long-term survivors, several scores were found significantly worse in patients with a stoma, in irradiated patients, and in those with carcinoma of the lower rectal third. In total, rectal carcinoma can be stated to be a chronic disease in 126 out of 219 curatively resected patients (57.5%).

**Conclusion:** Rectal carcinoma treatment has not finished after primary therapy. Recurrences and late adverse effects will occur in a relevant number of patients suffering from chronic disease. Adequate stage-related therapy has to be discussed in the tumor board and with the patient. Evaluation of late adverse effects and quality of life has to be integrated in quality management of treatment and cohort studies to improve long-term results. Cancer screening is the most reasonable procedure to avoid unsatisfying long-term consequences.

**P.27** CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND END-STAGE RENAL DISEASE ARE INDEPENDENT RISK FACTORS OF ANASTOMOTIC LEAKAGE AFTER SPHINCTER-PRESERVING SURGERY FOR RECTAL CANCER

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**Background:** Anastomotic leakage after sphincter-preserving surgery for rectal cancer is serious and has impacts on therapeutic results.

**Patients and method:** One hundred and seventy patients underwent curative sphincter-preserving surgery for UICC stage I-II rectal cancer was retrospectively analyzed. Univariate and multivariate analyses of characteristics of patient and tumor, details of treatment, clinical and oncological results were employed to identify risk factors for anastomotic leakage and therapeutic results.

**Results:** Anastomotic leakage occurred in 18 of 170 patients. By the univariate and multivariate analysis, risk of anastomotic leakage was significantly higher in patients with chronic obstructive pulmonary disease (COPD) (OR = 9.73) or end-stage renal disease (ESRD) (OR = 11.29). Anastomotic leakage resulted in higher postoperative mortality (P = .004), longer postoperative hospital stay (P < .001), poorer 5-year overall survival (P = .007), but comparable 5-year disease-specific survival (P = .451).

**Conclusion:** COPD and ESRD were demonstrated to be independent risk factors of anastomotic leaks after sphincter-preserving surgery for patients with rectal cancer. Eventually, anastomotic leakage significantly influenced postoperative mortality, postoperative hospital stay, and 5-year overall survival of these patients.

**P.28** MRI RE-STAGING AFTER RADIOCHEMOTHERAPY IN RECTAL CANCER: RESULTS AND LIMITATIONS OF TECHNIQUE

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**Objective:** The purpose of this study is to correlate MRI restaging of rectal cancer after radiochemotherapy (RCT) with pathology, and discuss limitations of MRI interpretation.

**Method:** MRI was performed after neoadjuvant treatment (45 Gy + 5-FU) and before surgery in all patients treated of rectal cancer between May 2006 and August 2009. MRI re-staging post RCT (T and N post RCT) and circumferential margin post RCT were compared with pathological staging after total mesorectal excision surgery.

**Results:** The sample included 30 patients (18 males, 12 females), mean age 59.7 years (42-75) receiving RCT. Tumors with complete regression after RCT were classified as T0. MRI T-stage distribution post RCT was T0: 20.7%, T1-2: 17.7%, T3: 62.1%. At pathology the distribution was ypT0: 23%, ypT1-2: 26.7%, ypT3: 50%. Overstaging was related to the difficulty in differentiating between viable tumor and fibrotic scar. Distribution of nodal stage after RCT was N0: 35.2%, N+ 44.4% and pathology distribution was ypN0:69%, ypN+31%. Overstaging was due to persistent sterilized nodes. Circumferential margin measured by MRI after RCT was a mean of 2.4 mm shorter than pathology and in 75% of cases the circumferential margin observed by MRI was coincident or shorter than pathology findings. Although A correlation of 0.64 was found between these two measures, two cases presented differences of -15 mm and 20 mm due to microscopic tumor foci in areas of fibrosis and sterilized fibrosis respectively.

**Conclusion:** Dowstaging and tumor response after RCT is evident in MRI and pathology. The most frequent problem of MRI interpretation after RCT is erroneously assigning a higher stage compared with pathology, being the reason that the image of fibrotic scar is misinterpreted as tumor. Nevertheless, in some cases with apparent very good image response, nests of tumoral cells persist inside the fibrotic scar. We thus conclude that it is better to overstage by image and to suppose that tumoral cells can persist in the scar when mesorectal excision is performed as it has more clinical impact: circumferential margin could be affected if the scar is not completely removed by the surgeon.
P.29 MULTISLICE CT VS MRI FOR THE ASSESSMENT OF TUMORAL STAGE IN RECTAL CANCER, BEFORE AND AFTER CHEMORADIOThERAPY

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1St Luc University Hospital, Brussels, Belgium; 2University Clinic of Mont Godinne UCL, Yvoir, Belgium

Objectives: To compare the staging accuracy between CT and MRI in patients with rectal cancer for the prediction of T, N stage, and the CRM measurement.

Material and method: We performed a retrospective analysis of 20 patients with CT and MRI examinations done before and after a long-course chemoradiotherapy. The T and N stages of CT and MRI as well as the CRM measurement were compared with pathological results of surgical specimen.

Results: The correlation of the T stage estimated with CT and MRI before and after radiochemotherapy with pathological results is respectively of 33 and 44 % and 44 and 39 % of the cases. The correlation of the N stage based on CT before and after radiochemotherapy and pathological results is respectively of 61 and 50 %. For the MRI, this correlation is respectively of 72 and 55 %. CT before and after radiochemotherapy correctly predicted the CRM respectively in 86 and 46 %, and MRI in 93 and 70 %.

Conclusion: The staging performances of multislice CT look lower than the staging performances of MRI. Nevertheless, in patients for whom MRI is not advisable, CT could be an alternative staging method with the best results in CRM estimation.

P.30 LOCAL STAGING OF ADENOCARCINOMA OF THE COLON WITH MULTISLICE CT

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1St Luc University Hospital, Brussels, Belgium; 2University Clinic of Mont Godinne UCL, Yvoir, Belgium

Objectives: To assess the staging accuracy of CT for the prediction of T, N stage, and vascular permeation, in patients suffered colon cancer.

Material and method: We performed a retrospective analysis of 30 patients with CT examinations done before surgery for colon cancer. T and N stages of CT were compared to pathological results of surgical specimen, as well as CT signs suggestive of vascular permeation. We evaluated by CT the short transverse axis (> 6 mm) of the local nodes, the contours (well or no defined), and the node’s homogeneity. We noted N0 if none of the previous CT signs were present, N1, when less than 3 nodes were abnormal and N2, if 3 or more abnormal nodes were observed . Two signs of vascular permeation were evaluated: (1) vascular tumoral contact and (2) spiculations at the outer border of the colic tumor.

Results: The correlation of the CT ‘T’ stage and pathological stage is 40 %. The global CT’s N stage correlated with pathological data is 47 %. When an heterogeneous node is observed on CT, it is associated with a pathological node invasion with a sensitivity of 71%, a specificity of 100%, a PPV of 100%, a NPV of 80%, and an accuracy of 87% (p<0.001).

Vascular permeation was correctly predicted with CT on the basis of worse defined outer tumoral contours with a sensitivity of 90%, a specificity of 20%, a PPV of 69%, and a NPV of 50% with an accuracy of 70% (p=0.05).

Conclusion: The T and N staging performances of multislice CT of colon adenocarcinoma as well as the observation of vascular permeation are poor compared to the pathological data.

P.31 MAGNETIC RESONANCE IMAGING ACCURACY IN ASSESSING TUMORAL STAGE AND REGRESSION AFTER CHEMORADIATION IN RECTAL CANCER

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Objectives: To assess the staging accuracy of MRI following chemoradiation in rectal cancer for the predicting criteria such as T and N stage, CRM and tumoral regression estimation.

Material and method: We performed a retrospective analysis of 24 patients with MRI examinations done before and after a long-course chemoradiotherapy. The T and N stages of MRI’s were compared to pathological results of surgical specimen, as well as the CRM measurement. We compared a grade of tumor regression (0 = no regression, 1 = intermediate regression, 2 = complete regression) to the Dworak grading system* and to a simplified pathological grading (0 = Dworak grade 0 or 1; 1 = Dworak grade 2 or 3; 2 = Dworak grade 4).

Results: The T stage predicted with post-chemoradiation MRI were statistically significantly correlated with pathological data (r = 0.404 ; p=0.054). The N stage were poorly correlated between MRI and pathological results (r=0.317 ; p=0.20). The CRM estimation with MRI was significantly correlated with the pathological findings (r = 0.480 ; p=0.011). The correlation between the MRI’s regression grade and the simplified pathological grade was poor (r=0.432 ; p=0.16) as well as the correlation between the MRI’s regression grade and the Dworak grade (r =0.387 ; p=0.13).


P.32 VALUE OF TUMOUR SIZE AS A PROGNOSTIC VARIABLE IN COLORECTAL CANCER: A CRITICAL REAPPRAISAL

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Objectives: Vertical tumour growth, reflected by T classification, represents the most important prognostic variable in colorectal cancer (CRC). Our study aimed to investigate the impact of tumour size, particularly the maximum tumour diameter, on outcome of affected patients.

Method: 400 patients (5%) of a total of 7564 patients were randomly sampled from the files of the CRC database of the Institute of Pathology, Medical University of Graz, Austria. Ultimately, 391 specimens were available for review pathology. Tumour size and location were extracted from the medical history and were known for 359 patients (94%). 107 tumours (28%) were located in the right colon, 110 (29%) in the left colon, and 164 (43%) in the rectum, respectively. Receiver-operator characteristic (ROC) analysis was applied to identify the optimal (maximum of sum of sensitivity and specificity) cut-off values with respect to prognostic impact.

Results: Median tumour size was 4.5 cm (range 0.6-15). Tumour size exceeding 4.5 cm was observed in 159 patients (44%) and was associated with high T and N classification, UIICC stage and tumour grade. At median follow-up of 59 months (mean 64 months, range 6-180), 141 patients (40%) showed tumour progression. While 4.5 cm was identified as the optimal prognostic cut-off value within the whole group of patients, ROC analysis restricted to different parts of the large bowel determined 5 cm, 5.3 cm, 3.9 cm, and 3.4 cm as cut-off values with the strongest discriminatory capacity in colon, right-sided colon, left-sided colon, and rectum cancers, respectively. Within the colon, tumour size exceeding 5 cm proved to be a significant prognostic variable in both univariate and multivariate analyses with respect to prediction of progression-free (RR 2.09, 95% CI 1.25-3.48, p=0.005) and cancer-specific (RR 1.86, 95% CI 1.08-3.21, p=0.025) survival. The prognostic impact was stronger in right-sided cancers than in left-sided cancers. Within the rectum, T classification, lymph node involvement, and tumour differentiation proved to be the only prognostic variables with respect to progression-free and cancer-specific survival, whereas for tumour size no independent influence on outcome was noted.

Conclusion: In conclusion, tumour size, in particular the maximum horizontal tumour diameter, proved to be an important prognostic parameter for patients with colorectal cancer. Optimal cut-off values vary among different parts of the large bowel, decreasing from the right colon to the left, and ultimately to the rectum. While prognostic impact is strong within the colon, it appears to be of minor value within the rectum. Since tumour size is significantly associated with progression-free and cancer-specific survival it may be of importance with respect to surveillance and selection of patients for adjuvant therapy. Further prospective studies, however, are warranted to validate the calculated cut-off values.

P.33 TUMOUR NECROSIS IS AN INDEPENDENT PROGNOSTIC VARIABLE IN COLORECTAL CANCER

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Objectives: The prognostic significance of tumour necrosis in colorectal cancer (CRC) still has to be defined. Our study aimed to analyze the prognostic value of tumour necrosis with respect to prediction of progression-free and cancer-specific survival and to relate findings to expression of proteins involved in the control of cancer cell death, such as p53 and bcl-2.

Method: 381 specimens were retrospectively re-evaluated. Follow-up data were available from 350 (92%) patients, mean and median time of follow-up being 64 and 61
RESULTS: Tumour necrosis was observed in 365 (96%) cases, with 180 (47%) cases showing focal necrosis, 119 (31%) moderate necrosis, and 66 (17%) extensive necrosis, respectively. Extent of necrosis was significantly associated with high T classification (p<0.001), high N classification (p=0.005), high UICC stage (p<0.001), poor tumour differentiation (p<0.001), large tumour size (p<0.001), and presence of blood vessel invasion (p<0.001). With respect to TMA analysis, cancer tissue allowing a reliable evaluation of p53 and bcl-2 immunoreactivity was present in 368 (97%) cases. Distinct nuclear p53 immunoreactivity was observed in 192 (52%) tumours, whereas distinct cytoplasmic bcl-2 expression was present in 95 (26%) tumours. No association of tumour necrosis with immunohistochemical expression of p53 and bcl-2 was observed. In Kaplan-Meier analyses using cut-off values of 10% and 50% for assessment of tumour necrosis, prognostic impact was observed regarding both progression-free and cancer-specific survival (p<0.001, respectively). Multivariate testing, however, proved only the 30% cut-off value (extensive necrosis) as independent predictor of both disease progression and cancer-specific survival in a model including a variety of established prognosticators, such as T and N classification as well as tumour grade. However, restricting analysis to UICC stage II patients, the 10% cut-off value for tumour necrosis proved to be an independent prognostic variable with respect to progression-free, yet not with respect to cancer-specific survival.

CONCLUSION: Tumour necrosis proved to be an independent variable with respect to progression-free and cancer-specific survival. Its presence is readily assessable in H&E stained sections, and should therefore routinely be commented upon in the pathology report. To assess the value of tumour necrosis as selection criterion for adjuvant treatment future prospective trials are warranted.

P.34 PROLACTIN RECEPTOR EXPRESSION IN COLORECTAL CANCER - THERAPEUTIC OPTION FOR AFFECTED PATIENTS

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OBJECTIVES: Over the past two decades prolactin (PRL) and its receptor, the prolactin receptor (PRL-R), have been controversially discussed in colorectal cancer (CRC). Recent data indicates that PRL-R expression by immunohistochemistry using a tissue microarray technique and recorded as either positive (using a cut-off value of 10%) or negative.

METHOD: 373 primary CRC and 171 corresponding metastases were evaluated for PRL-R expression. Immunohistochemical expression of p53 and bcl-2 was assessed using a tissue microarray technique and recorded as either positive (using a cut-off value of 10%) or negative. PRL-R expression was semiquantitatively scored as either focal (<10% of tumour cells positive), moderate (10-50%), or extensive (>50%). PRL-R expression was observed in 360 out of 373 (97%) primary tumours, with 21 (6%) cases showing focal, 55 (15%) moderate and 284 (76%) extensive expression, respectively. Extensive PRL-R expression was significantly associated with high T classification (p<0.001), high N classification (p<0.001), wide UICC stage (p<0.001), poor tumour differentiation (p<0.001), large tumour size (p<0.001), and presence of blood vessel invasion (p<0.001). With respect to TMA analysis, cancer tissue allowing a reliable evaluation of PRL-R expression was present in 368 (97%) cases. Distinct nuclear PRL-R immunoreactivity was observed in 192 (52%) tumours, whereas distinct cytoplasmic bcl-2 expression was present in 95 (26%) tumours. No association of tumour necrosis with immunohistochemical expression of p53 and bcl-2 was observed. In Kaplan-Meier analyses using cut-off values of 10% and 50% for assessment of tumour necrosis, prognostic impact was observed regarding both progression-free and cancer-specific survival (p<0.001, respectively). Multivariate testing, however, proved only the 30% cut-off value (extensive necrosis) as independent predictor of both disease progression and cancer-specific survival in a model including a variety of established prognosticators, such as T and N classification as well as tumour grade. However, restricting analysis to UICC stage II patients, the 10% cut-off value for tumour necrosis proved to be an independent prognostic variable with respect to progression-free, yet not with respect to cancer-specific survival.

CONCLUSION: Tumour necrosis proved to be an independent variable with respect to progression-free and cancer-specific survival. Its presence is readily assessable in H&E stained sections, and should therefore routinely be commented upon in the pathology report. To assess the value of tumour necrosis as selection criterion for adjuvant treatment future prospective trials are warranted.

P.35 RECTAL CANCER: OVERALL EXPERIENCE WITH MRI AND RADIOGRAPHICAL US IN T1-3 STAGE, CIRCUMFERENTIAL MARGIN PREDICTION AND EVALUATION OF TUMORAL RESPONSE AFTER NEOADYUVANT TREATMENT IN A MULTIDISCIPLINARY GROUP

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OBJECTIVES: Since 2006 the patients treated of rectal cancer were staged with pelvic MRI rectal US and thoracic-abdominal CT. The objective is to analyse the experience acquired and the results of image findings compared with pathology.

METHOD: MRI is performed by 2 radiologists and US by 6 surgeons. Both techniques were done at the moment of diagnosis and after chemoradiotherapy (CRT) in those who received it. Circumferential margin (CM) was estimated by MRI and TNM with MRI, US and CT. Total mesorectal excision surgery was performed. Data of radiological staging, treatment and pathology were collected prospectively and analysed with SPSS. Concordance between MRI and US with pathology staging and CM has been studied only in the no CRG group. Tumoral regression (TR) was studied in the CRT group and measured by MRI and in the specimen. Radiological and pathological responses were compared.

RESULTS: 84 patients were diagnosed of rectal cancer. Mean of age was 62.7 years and 71.4% were males. 69%patients received CRT. Actually, 73 patients have been operated. Sensibility (SE) of US to predict T3 stage vs. T2 or less was 50%, specificity (SP) 33% positive predictive value (PPV) 63% and negative predictive value (NPV) 55%. MRI SE for T3 prediction was 75%, SP 73%, PPV 82% and NPV 73%. In nodal staging, US SE to predict N+ was 50%, SP 57%, PPV 50% and NPV 72%. For MRI the results were 79% of SE, 44% of E, 52% PPV and 73% NPV. The capacity TO estimate CM with MRI was very high. A Mean 0.2 mm of difference between MRI and pathological specimen was found in no pre CRT (p=0.012) with a correlation of 0.65 (p=0.03). In radiated patients the CM estimated with MRI was 3.94 mm shorter than pathology (p=0.003), correlated with tumoral regression. Pathological TR was over 70% in half of cases, but only over 50% (median). In MRI, the prediction of tumoral regression with MRI depended on the size reduction of the tumour. In a restricted group of patients with a clear size reduction of tumour observed by MRI, the mean of radiological tumoral regression WAS 63% and the pathology WAS 69.1%. This difference of 7.88% less regression seen in MRI (p=0.434) rises to 22.9% of less MRI regression (p=0.003) if all cases were included.

CONCLUSIONS: Our results are different than previously published. MRI differentiates better than US between T3 and T2-T1. The reasons are a shorter learning curve for MRI, easier interpretation and greater radiological experience. SE and SP for N stage are similar to the literature. The ability of MRI to predict the CM is very accurate with high concordance in few cases. The ability of MRI to estimate tumor regression depends on the degree of regression associated to decrease in size. Radiological RT is very close to pathological when clear size differences before and after CRT. When there is no clear size reduction, pathologic TR is greater than the radiological TR because RT may be due to decrease cellularity in the tumor scar.
Purpose: To assess the value of diffusion weighted MRI (DW-MRI) before, during and after preoperative chemoradiotherapy (CRT) in patients with locally advanced rectal cancer for early response prediction and presurgical evaluation.

Material and method: DW-MRI was performed, prior to CRT, after 10-12 fractions and 5 weeks after the end of CRT (45 Gy; 1.8Gy/fraction + concomitant 5-fluorouracil (225mg/m²)) in 17 patients with pathologically confirmed rectal cancer (51 MRI examinations). Lesions were quantitatively assessed by manual delineation of regions of interest (ROI) around the tumors on the native DWI images with b-values ranging from b0 to b1000, from which the ADC was calculated for both the pretreatment and per-treatment examinations. Additionally the b1000 signal intensity (b1000-SI) of lesions after the end of CRT were quantitatively assessed and normalized to the SI of non-tumoral rectal wall (b1000-SI(ratio)). Change in ADC (ΔADC) and b1000-SI(ratio) were correlated to the histopathological findings after TME-surgery (Dworak regression grade and pathologic complete response (pCR)).

Results: DW-MRI during and after CRT showed a significantly lower ΔADC in lesions with Dworak grade 0-2 versus Dworak grade 3-4 (during CRT: ΔADC=0.100.09 versus 0.490.19; p<0.0001 and post-CRT: ΔADC=0.150.12 versus 0.650.13; p<0.0001) and also a significantly lower ΔADC in lesions that did not reach pCR compared to lesions that did (during CRT: ΔADC=0.150.12 versus 0.650.13; p<0.0001 and post-CRT: ΔADC=0.180.17 versus 0.820.42; p=0.01). Based on ROC-analysis an optimal threshold (in %) of 25 and 40 was found for the ΔADC during CRT to differentiate Dworak grade 0-2 from Dworak grade 3-4 and pCR from no pCR. For the ΔADC after CRT a threshold of 34% respectively 48% was found. Additionally the b1000-SI(ratio) at the post-CRT MRI examination was significantly lower in lesions with pCR versus lesions that did not reach pCR (b1000-SI(ratio): 0.930.11 versus 1.640.11; p<0.0001). An optimal threshold of 1.2 was determined.

Conclusions: These preliminary data show the ability of DW-MRI to predict the CRT induced tumor regression early on during neoadjuvant treatment using the ΔADC. This would allow adaptation of treatment. Secondly we have shown the ability of DW-MRI, using b1000-SI(ratio) to differentiate lesions with a complete pathological response from incomplete responders at the time of surgery. DW-MRI may be a helpful tool in deciding in which patients TME surgery could be avoided.
P.37 IMAGING FOR COLORECTAL LIVER METASTASES - A META-ANALYSIS
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Abstract purpose: To perform a meta-analysis to obtain on a per-patient and per-lesion basis sensitivity estimates of state of the art computed tomography (CT), magnetic resonance (MR) imaging, fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) and PET/CT for the detection of colorectal liver metastases.

Materials and method: The MEDLINE and EMBASE databases were searched for relevant original articles published from January 2004 to October 2009 on CT, MR imaging, FDG-PET and PET/CT for the detection and characterization of colorectal liver metastases.

Criteria for inclusion were: prospective study; study population >10 patients; histopathologically proven primary colorectal carcinoma; diagnostic imaging was performed to identify and characterize liver lesions; intra-operative findings, histopathology and/or follow-up were used as reference standard; contingency table could be constructed. Raw data was documented and sensitivity and specificity estimates were calculated on a per-patient basis for the four different modalities. Sensitivity estimates were calculated on a per-lesion basis. All analyses were based on nonlinear mixed-effects approach.

Results: The internet-search yielded a total of 5890 articles, of which 24 fulfilled all inclusion criteria. The included studies evaluated 2613 patients (57% male, 43% female) with a mean age of 62.1 years (range: 23 - 93 years). Sensitivity estimates on a per-patient basis for helical CT, 1.5-T MR imaging, FDG-PET and PET/CT were 80.7 % (95 % CI; 60.4 - 91.9), 67.1 % (95 % CI; 59.5 - 73.9), 95.4 % (95 % CI; 93.2 - 97.0) and 96.8 % (95 % CI; 94.6 - 98.2), respectively (Fig. 1). FDG-PET and PET/CT were the most accurate modalities; differences were significant (all p < 0.05) compared to helical CT and MR imaging. On a per-patient basis, specificity estimates for helical CT, 1.5-T MR imaging, FDG-PET and PET/CT were 88.7 % (95 % CI; 50.5 - 98.4), 92.9 % (95 % CI; 89.9 - 95.1), 91.7 % (95 % CI; 86.0 - 95.2) and 96.2 % (95 % CI; 91.3 - 98.4) (Fig. 2). Differences between the modalities were not significant (all p > 0.05). On a per-lesion basis, sensitivity estimates for helical CT, 1.5-T MR imaging, FDG-PET and PET/CT were 70.0 % (95 % CI; 65.5 - 74.2), 87.3 % (95 % CI; 82.0 - 91.2), 75.2 % (95 % CI; 58.6 - 86.7) and 58.0 % (95 % CI; 47.1 - 68.2), respectively (Fig. 3). MR imaging had the highest sensitivity; differences compared to the other modalities were significant (all p < 0.05).

Conclusion: FDG-PET and PET/CT have the highest sensitivity estimates on a per-patient basis, but MR imaging has the highest sensitivity on a per-lesion basis. All sensitivity estimates, except for MR imaging, were lower on a per-lesion basis compared to the sensitivity estimates on a per-patient basis. Specificity estimates on a per-patient basis were comparable between the four modalities.

P.40 TRANSCRIPTIONAL PROFILE OF WNT SIGNALING COMPONENTS DURING COLORECTAL CANCER PROGRESSION
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Objectives: Aberrant Wnt pathway signaling due to mutations in key regulators of this pathway is an early progression event in the majority of colon cancers. In most colorectal tumors it occurs through APC mutation that stabilizes β-catenin and allows Wnt signaling via abnormal accumulation of free β-catenin in the nucleus. However, the downregulation of some components of Wnt signaling during early stages of colorectal tumorigenesis indicates more complex role of Wnt signaling. We examined therefore gene expression profiles of selected components of Wnt signaling pathway and Eph receptors, the Wnt signaling target genes that play a role in colorectal cancer progression.

Method: Tissue samples of carcinoma and adenoma were studied using quantitative RT-PCR and TaqMan probes. Carcinoma samples were obtained from randomly collected surgical specimens from patients who underwent surgery for colorectal cancer. As control tissue were used samples from macroscopically normal colonic mucosa of resection margins. The samples of colon adenomas were obtained.

Figure 1. Per-patient sensitivity with 95 % confidence intervals.

Figure 2. Per-patient specificity with 95 % confidence intervals.

Figure 3. Per-lesion sensitivity with 95 % confidence intervals.
endoscopically whereas the control healthy tissue represented biopsy specimens of macroscopically and microscopically normal colonic mucosa from patients who underwent endoscopy for reasons other than IBD diagnosis and cancer screening. The mRNA transcripts of the following genes were measured: axin 1, axin 2, β-catenin, β-transducin repeat containing protein (β-TrCP), LDL-receptor related protein 5 (LRP5), transcription factors TCF1 and TCF4, the Ephrin receptors EphB1, EphB2 and EphB3, and the inhibitors of Wnt/β-catenin signaling - naked cuticle homologue 1 (NKD1), secreted Frizzled-related protein 1 (sFRP1), and the inhibitors of Dickkopf family (DKK1, DKK2, DKK3).

Results: In patients with colorectal cancer, the neoplastic tissue showed upregulation of transcripts for axin 2, DKK1 and downregulation of Wnt/β-catenin signaling - nucleated cuticle homologue 1 (NKD1), secreted Frizzled-related protein 1 (sFRP1), and the inhibitors of Dickkopf family (DKK1, DKK2, DKK3).

Conclusion: In patients with colorectal cancer, the neoplastic tissue showed upregulation of transcripts for axin 2, DKK1 and downregulation of Wnt/β-catenin signaling - nucleated cuticle homologue 1 (NKD1), secreted Frizzled-related protein 1 (sFRP1), and the inhibitors of Dickkopf family (DKK1, DKK2, DKK3).

P.4.2 ASSOCIATION BETWEEN MICROSATELLITE INSTABILITY AND VASCULAR ENDOTHELIAL GROWTH FACTOR A IN COLORECTAL CANCER

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Objectives: Colorectal neoplasms with or without microsatellite instability (MSI) represents distinctive pathological characteristics, and it has been suggested that they stimulate angiogenesis in different ways. The vascular endothelial growth factor (VEGF) system is essential for the angiogenic process and the growth of malignant tumours. The previous reports have primarily focused on the VEGF-A expression in tumour tissue assessed by immunohistochemistry (IHC), and the literature on the relationship between the MSI status and quantitative measures of circulating VEGF-A is very limited. The aim of this study was to investigate the possible relationship between MSI status and the levels of circulating VEGF-A in patients with colorectal cancer (CRC).

Method: MSI status and serum VEGF-A levels were analyzed in a test cohort of 83 patients surgically resected for adenocarcinomas of the colon or rectum between 2004 and 2005. Associations were validated in a second independent cohort of 173 patients with CRC, operated between 2005 and 2008. MSI was determined using IHC. Tumours lacking protein expression of any of the four mismatch repair genes (MLH1, PMS2, MSH2, or MSH6) was labelled as high MSI (MSI-H). The rest was considered microsatellite stable (MSSS). The tumours of 16 patients in the test cohort and 28 patients in the validation cohort were classified as MSI-H. The serum VEGF-A protein analysis was performed using the ELISA technique.

Results: In the test cohort, we found that patients with MSI-H tumours had significantly higher median VEGF-A levels, 617 pg/ml (95% CI 445–863), compared to the patients with MSS tumours, 329 pg/ml (95% CI 227–506), p=0.01. In the validation cohort, patients with MSI-H tumours still presented with significantly higher median VEGF-A levels, 436 pg/ml (95% CI 240–590), compared to the patients with MSS tumours, 283 pg/ml (95% CI 235–333), p=0.04.

Conclusion: In two independent cohorts, patients with MSI-H tumours presented with significantly higher levels of serum VEGF-A. If further validated, these findings could be of importance when considering the effect of anti-VEGF-A treatment such as bevacizumab. Patients with MSI-H tumours might benefit differentially form such treatments compared to patients with MSS tumours.

P.4.3 HIGH SENSITIVE METHODS TO IDENTIFY K-RAS MUTATIONS INCREASE THE DETECTION OF NON-RESPONDER METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH ANTI-EGFR MONOCLONAL ANTIBODIES

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Objectives: K-Ras mutations represent the major cause of resistance to anti-EGFR monoclonal antibodies (MoAbs) in metastatic colorectal cancer (mCRC) patients. Although K-Ras test is now mandatory for the selection of patients eligible to be treated with anti-EGFR MoAbs, standardized techniques for K-Ras analysis are lacking as well as the sensitivity of K-Ras test has to be yet determined. We evaluated whether more sensitive methods for K-Ras analysis than direct sequencing could improve the prediction of anti-EGFR MoAbs efficacy.

Method: We retrospectively evaluated objective tumor response in 53 mCRC patients treated with cetuximab or panitumumab. K-Ras mutational status was based on direct sequencing, MALDI-TOF Mass Spectrometry (MS), mutant-enriched PCR (ME-PCR) and engineered mutant-enriched PCR (eME-PCR), which have a sensitivity of about 20%, 10%, 0.01% and 0.01%, respectively. In addition, we investigated BRAF and PIK3CA gene mutations by direct sequencing, and PTEN protein expression by immunohistochemistry.

Results: Partial response was observed in 11/53 (21%) cases. Direct sequencing revealed K-Ras mutations in 17/53 (32%), BRAF mutations in 4/53 (7%), and PIK3CA mutations in 4/53 (7%). PTEN loss was identified in 17/53 (33%) cases. All these alterations were restricted to non-responders patients.

Thirty-two patients with K-Ras and BRAF wild-type status were analyzed for K-Ras mutational analysis using a high sensitive methods. We detected additional K-Ras mutations in 4/32 (12%) cases by MALDI-TOF MS, in 3/32 (22%) by ME-PCR and in 9/32 (28%) by...
MG1 and 177Lu-UPC10 resulted in a transient decrease in body weight, compared to a maximum 3 days post injection (see Figure 1). The tumour-to-blood ratio of 111In-MG1 preferentially accumulated in tumour lesions in the liver reaching 0.3 x 10^6 CC531 tumour cells. After 10 days the liver tumours were treated with RFA.

The survival curves of the group that received 177Lu-UPC10 and the group that received saline only did not differ (P=0.886) (see Figure 2). Administration of RIT immediately after surgery improved survival significantly compared to administration of the control antibody (hazard ratio (HR) 1.71, P=0.027). A therapeutic efficacy of delayed treatment seemed likely (HR 2.34, P=0.055). Survival after early administration did not differ from delayed administration (HR 1.16, P=0.763).

Conclusion: This study provides proof of principle that radioimmunotherapy can be an effective adjuvant treatment modality after surgical treatment of colorectal liver metastases.

P.44 PROGNOSTIC IMPACT OF MICRONRNA-RELATED GENES POLYMORPHISMS ON SURVIVAL OF PATIENTS WITH COLORECTAL CANCER

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Purpose: Polymorphisms in microRNA (miRNA) machinery genes and miRNA-containing genomic regions may play an important role in cancer development and prognosis. Accordingly, the present study analyzed 40 single nucleotide polymorphisms (SNPs) of miRNA-related genes and their impact on the prognosis for patients with colorectal cancer.

Patients and method: Four hundred and twenty-six consecutive patients with surgically treated colorectal adenocarcinoma were enrolled in the present study. The genomic DNA was extracted from fresh colorectal tissue and 40 polymorphisms of DNA repair genes determined using a real-time PCR genotyping assay.

Results: In the univariate analysis, the progression-free survival (PFS) of the patients with the combined mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/G genotype (mir492 C/G) (P value=0.0426), while overall survival was not significantly different. However, no association was noted between SNPs of miRNA-related gene evaluated and survival in multivariate analysis including age, site of the disease, differentiation, CEA level, and stage.

Conclusion: The 40 polymorphisms in miRNA-related genes were not found to be an independent prognostic marker for Korean patients with surgically resected colorectal cancer. However, further studies are warranted to clarify the role of miRNA-related genes polymorphisms as a prognostic biomarker for colorectal cancer patients.

P.45 ADJUVANT RADIOIMMUNOTHERAPY IMPROVES SURVIVAL OF RATS AFTER RESECTION OF COLORECTAL LIVER METASTASES

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Objectives: Half of the patients with colorectal cancer develop liver metastases during in the course of their disease. Although partial hepatectomy can improve 5-year survival to about 30%, recurrent tumour growth in the liver occurs frequently. The aim of the present study was to test the hypothesis that adjuvant radioimmunotherapy (RIT) might be an effective way to prevent recurrent liver metastases after partial hepatectomy in an experimental model.

Method: Male Wag/Rij rats underwent a mini-laparotomy with intrhepatic injection of 0.3 x 10^6 CC531 tumour cells. The biodistribution of 111In-labelled MG1 after intravenous administration was determined at 1, 3 and 7 days after injection and visualized by gamma-camera imaging. The therapeutic efficacy of 177Lu-MG1 (300 MBq/kg) was compared with that of an irrelevant antibody (UPC10) labelled with the same activity dose of Lu-177 and saline only. RIT was administered either at the day of the tumourectomy (day 14) or 7 days later. Primary endpoint was survival.

Results: 111In-MG1 preferentially accumulated in liver reaching a maximum 3 days post injection (see Figure 1). The tumour-to-blood ratio of 111In-MG1 increased with time, reaching 19 ± 2 at day 7. Both the administration 177Lu-MG1 and 177Lu-UPC10 resulted in a transient decrease in body weight, compared to administration of saline only. No other signs of clinical discomfort were registered. The survival curves of the group that received 177Lu-UPC10 and the group that received saline only did not differ (P=0.886) (see Figure 2). Administration of RIT immediately after surgery improved survival significantly compared to RIT administered either at the day of the tumourectomy (day 14) or 7 days later. Although partial hepatectomy can improve 5-year survival to about 30%, recurrent tumour growth in the liver occurs frequently. The aim of the present study was to test the hypothesis that adjuvant radioimmunotherapy might be an effective way to prevent recurrent liver metastases after partial hepatectomy in an experimental model.

Conclusion: This study provides proof of principle that radioimmunotherapy can be an effective adjuvant treatment modality after surgical treatment of colorectal liver metastases.

P.46 ADJUVANT RADIOIMMUNOTHERAPY AFTER RADIOFREQUENCY ABLATION OF COLORECTAL LIVER METASTASES

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Objectives: Half of the patients with colorectal cancer develop liver metastases somewhere in the course of their disease. Radiofrequency ablation (RFA) has shown to improve survival in patients not suitable for surgical resection of the metastases. However, recurrences after RFA are a major problem. Radioimmunotherapy has shown to improve outcome after resection of liver metastases. Therefore, the present study was to test the hypothesis that adjuvant radioimmunotherapy might be an effective way to prevent recurrent liver metastases after RFA of liver metastases in an experimental model.

Method: Male Wag/Rij rats underwent a mini-laparotomy with intrhepatic injection of 0.3 x 10^6 CC531 tumour cells. After 10 days the liver tumours were treated with RFA.
The therapeutic efficacy of $^{177}$Lu-MG1 at the maximal tolerable dose (300 MBq/kg) was compared with that of no adjuvant treatment. Radiosinmunotherapy was administered either at the day of RFA (day 10) or 7 days later. Primary endpoint was survival. An interim-two-month survival analysis was made.

Results: Administration $^{177}$Lu-MG1 resulted in a transient decrease in body weight, compared to no adjuvant treatment. However, no signs of clinical discomfort were registered. Two-month survival rate in the untreated group was 65%. Two-month survival rate was 90% in the group treated with $^{177}$Lu-MG1 on the day of RFA (P = 0.039 as compared to the untreated group). Two-month survival rate was 75% in the group treated with $^{177}$Lu-MG1 7 days after the RFA procedure (P = 0.278 as compared to the untreated group).

Conclusion: This study provides proof of principle that radiosinmunotherapy can be an effective adjuvant treatment modality after radiofrequency ablation of colorectal liver metastases and should be administered shortly after the procedure.

Figure 1. Survival curves at two months after RFA.

P.48 MGMT -535G>T POLYMORPHISM IS ASSOCIATED WITH PROGNOSIS FOR PATIENTS WITH METASTATIC COLORECTAL CANCER TREATED WITH OXALIPLATIN-BASED CHEMOTHERAPY

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Purpose: 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.

Patients and method: 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.

Results: In a logistic regression analysis adjusted to age, sex, primary site, disease status, and regimen, the POLR2E (rs4937) and MSH2 (rs72185) polymorphisms were significantly associated with the response to the oxaliplatin-based chemotherapy among the 60 patients assessable for response. Plus, a multivariate survival analysis showed that the MGMT (rs1050450) -535G>T polymorphism was significantly associated with progression-free survival (PFS), where the TT genotype was found to correlate with a worse PFS than the GG genotype (HR = 3.22, 95%CI = 1.49-7.116, p = 0.004). For the clinical parameters, curative resection was also a significant prognostic factor in a Cox model for PFS and overall survival (OS) (HR = 0.234 and 0.263, p<0.001 and 0.018, respectively).

Conclusion: The MGMT (rs1050450) -535G>T polymorphism was found to be correlated with PFS in patients with advanced colorectal cancer treated with oxaliplatin-based chemotherapy.

P.49 A SIMPLE IMMUNOMAGNETIC ENRICHMENT SYSTEM FOR DETECTING HUMAN CIRCULATING COLORECTAL CANCER CELLS

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Background: The detection of tumor cells in the peripheral blood (CTCs) has greatly increased interest in the last decade. Their count and characterization give important prognostic information in pts with advanced colorectal cancer and might also help to tailor systemic therapies. Being the expected number of CTCs very low, the utilized technical/methodological approaches are crucial.

Materials and method: Here we describe the development of a simple, low-cost procedure, capable of efficient and selective separation of CTCs from peripheral whole blood, without requisite pre-labelling or processing of samples, developed in our laboratory. As immuno-labelling capture procedure, we focused on EpCAM isolated intact cells, staining positive for cytokeratins and negative for CD45. The second labelling step has been performed by means of a Dynal magnetic beads (Invitrogen) whose peculiar characteristic is to be directly visible by light microscopy. SNU-C2B and SW-480 colorectal cancer cell lines with different levels of EGFR expression were used in spiking experiments.

Results: The innovative step of the method is the possibility to perform the entire procedure in a multilwells plate and to directly observe and count the separated cells at the bottom of the wells. This is allowed by a dedicated magnetic plate fitting the shape of the disposable standard 8 multilwells plate. In this way is possible to directly monitor each labelling step as well as the final CTC recovery by a simple staining with Propidium Iodide. Our approach successfully identified colorectal ancer cells diluted in the peripheral blood with a range of 2-5 CTCs per ml and approximately 50% purity.

Conclusions: Our refined immunomagnetic enrichment assay provides an effective tool for an accurate identification of CTCs. It also allows a combination with automated microscopic and microchip-based techniques as well as a characterization of CTCs for other antigens (i.e. EGFR expression) in order to generate clinically important information for colorectal cancer pts.
**P.50 ASSOCIATION OF JC VIRUS DNA SEQUENCES WITH COLORECTAL CANCER - PRELIMINARY RESULTS**

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**Objective:** The human polyomavirus JC (JCV) is a small DNA virus known to possess oncogenic potential. An association between JC virus and human cancers is suspected and this virus has been documented in colorectal cancer (CRC). However, some researchers question the role of JCV for the development of neoplasms as they fail to detect the virus. Our objective was 1. To determine whether genomic sequences of JCV can be indentified in the patients with CRC; 2. To evaluate the melting curve pattern of the positive samples.

**Method:** We examined biopsy tissues from CRC (n=17) and adjacent normal colonic mucosa from the resection lines. Adenomatous polyps were also studied (n=3) where present. DNA was extracted from the collected probes for the detection of JCV gene sequences. SYBR Green real-time polymerase chain reaction amplifications were performed using gene-specific primers for the viral T-antigen. All reactions were followed by dissociation analysis in order that a melting temperature was determined. Clinical and morphological characteristics of the patients were collected.

**Results:** Three of 17 cancer samples harbored JC virus sequences and three more had a melting curve pattern shifted by approximately 1.5°C, suggesting differences in their sequence. Two polyps were determined positive and one more had the same shifted dissociation profile. Four of the adjacent normal mucosa specimens were recognized as positive.

**Conclusion:** The presence of JCV DNA sequences in CRC enriches the controversy over the role of this virus in human malignancies, whose clarification is in need of further molecular and epidemiological studies. Our findings confirm a possible role of this polyomavirus in the pathogenesis of CRC. We discuss the suspected mechanisms of viral induced oncogenesis, briefly review previous studies, the implication of this knowledge for new therapeutic strategies and as a possible prognostic factor.

**P.51 SURVIVAL IMPACT OF K-RAS AND PIK3CA MUTATIONS IN STAGE III COLON CARCINOMA**

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**Objective:** Molecular markers could help to make a more accurate classification of colon cancer. Mutations in several genes influence disease progression and could therefore influence treatment of colon cancer patients. We aimed to study the prognostic value of several mutations in the K-ras gene and the PIK3CA gene in a homogenous group of stage III colon cancer patients treated with 5-FU based monotherapy.

**Method:** Two hundred and nine patients were included in this study. They were all diagnosed as stage III colon cancer patients treated with surgery followed by 5-FU based monotherapy. DNA was isolated from tumor areas selected by an experienced pathologist and macrodisseected. K-ras mutations in codons 12 and 13 were determined by PCR followed by sequencing and confirmed by single nucleotide primer extension. Mutations in exons 9 and 20 of the PIK3CA gene were determined by PCR followed by single nucleotide primer extension. In addition, MSI status of all patients was also determined by PCR and fragment size analysis.

**Results:** K-ras was mutated in 35% of the patients, 14% was MSI positive. Mutations on K-ras correlated significantly with the development of distant metastasis or local recurrence (p=0.014). There were no further significant associations between the carriage of a K-ras mutation and other variables. K-ras mutation had no significant prognostic value in this group of patients. PIK3CA mutational analysis is ongoing and will be presented.

**Conclusions:** Differently than stage IV colon cancer patients, mutations in the K-ras gene have no prognostic or predictive value on stage III colon cancer patients. However, the carriage of these mutations is associated with disease progression. Further investigation of the mutational status other members of the Akt pathway like PIK3CA could explain this association, as they are also associated with disease progression.

**P.52 ACTIVATING KRAS MUTATIONS AS AN INDEPENDENT PREDICTOR IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH CETUXIMAB**

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**Objective:** Cetuximab, a monoclonal antibody targeting epidermal growth factor receptor (EGFR), has been proven to be efficient in metastatic colorectal cancer (mCRC); however, the therapeutic response is variable and markers predictive of response are urgently required. This study was conducted to determine the predictive values of KRAS mutation status in mCRC patients treated with cetuximab plus chemotherapy.

**Method:** Ninety-five mCRC patients receiving cetuximab plus the FOLFOX or FOLFIRI chemotherapy were enrolled into the present study. KRAS mutation status were analyzed using direct sequencing. The association between clinical response, progression-free survival (PFS) and overall survival (OS) as well as KRAS mutation status were evaluated.

**Results:** Of 95 mCRC patients, KRAS mutations were identified in 41 cases. Among 41 tumors with KRAS mutation, 33 were found to be activating mutants at codons 12, 13, 15 or 18, while 8 were non-activating mutants at codons 20, 30 or 31. Patients with tumors that harbor wild-type KRAS are more likely to have a better PFS and OS when treated with cetuximab plus chemotherapy (all P < 0.05). Furthermore, patients with non-activating KRAS mutants in tumors had a significantly better PFS and OS than patients with activating KRAS mutants (both P < 0.05).

**Discussion:** The study suggests that activating KRAS mutants is an utmost important independent predictive marker in mCRC patients treated with cetuximab plus chemotherapy; of which activating KRAS mutations could help to identify the subgroup of patients who are most likely to respond to cetuximab plus chemotherapy.

**P.53 ANNEXIN AND SURVIVIN MRNA EXPRESSION IN LOCALLY ADVANCED RECTAL CANCER AS A SIGN OF RESISTANCE TO PREOPERATIVE CHEMORADIATION**

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**Background:** Preoperative chemoradiation is widely used to improve local control in patients with locally advanced rectal cancer. Some recent studies have shown that Annexin and Survivin are involved in the resistance capability of tumours to chemoradiation. In the present study we investigated whether Survivin or Annexin A4 and A5 expression could predict response to preoperative chemoradiation.

**Material and method:** Biopsies of untreated tumour and normal rectal tissue cancer were taken from 38 patients with locally advanced rectal cancer (clinical stages cT3/4N0 or T2N1) before the start of neoadjuvant chemoradiotherapy including Capecitabine, Irinotecan and Cetuximab. Samples of normal and tumour tissues were also collected during surgical resection after chemoradiation. Expression of Annexin and Survivin was measured by real-time Polymerase chain reaction (RT-PCR) in normal and tumour tissue before and after chemoradiation. We then compared the individual expression results of normal and tumour tissue to the downstaging grades of those patients. Responders were defined as having a histopathological staging ypT0-2 ypN0 and non-responders ypT3-4 or ypN1/2. We also compared the individual progression-free survival with the expression rate of surviving and annexin A4 and A5.

**Results:** The expression levels of pretreatment Survivin and Annexin A4 and A5 are significantly lower in normal than in tumour tissue (p<0.001). Pretreatment tumour and normal tissue showed neither concerning Survivin nor Annexin A4 and A5 expression could predict response to preoperative chemoradiation.

**Conclusion:** In our collective, we saw no different expression levels of Survivin, Annexin A4 or Annexin A5 correlated to downstaging effects. Survivin is an inhibitor of apoptosis protein and plays a key role in the regulation of apoptotic under chemoradiation it changes the expression in the tumour tissue significantly different between responders and non-responders. This might be a predictive or prognostic value that due to the small number of patients we were not able to show. Additional studies are necessary to further define the role of Survivin, Annexin A4 and Annexin A5 as potential predictors of neoadjuvant treatment response in rectal cancer undergoing neoadjuvant radiochemotherapy.
P.54 THE EGFR SP1-216 GENE POLYMORPHISM HAS AN INDEPENDENT PROGNOSTIC VALUE IN LOCALLY ADVANCED RECTAL CANCER TREATED WITH PREOPERATIVE CHEMORADIATION

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Background: Advanced surgery and development of intensive schedules of preoperative combined chemoradiation to patients with a high risk of local recurrence have reduced the rate of recurrence and improved survival. Unfortunately, a subgroup of patients is still inadequately treated and despite an excellent tumour response, some will eventually die from distant metastasis. These patients may benefit from postoperative systemic treatment, and consequently reliable prognostic markers are needed. The aim of the present study was to evaluate the prognostic value of three germ line polymorphisms (The EGFR Sp1-216, TS and EGF A61G polymorphisms) with potential impact in the event of local or regional failure, in locally advanced T3 and T4 tumour treated with long-course preoperative CRT.

Method: Patients were treated with preoperative CRT (external total dose of 60 Gy by S-fold conformal technique, +/- an intracavitary fraction of 5 Gy to the tumour bed) and concomitant oral Ufortal (Merk KGA, Darmstadt, Germany) 300mg/m2 daily and Leukovorin 22.5mg/per day five days a week. Genomic DNA was extracted from whole blood and genotype analysis was performed by PCR and results were verified by sequencing. Cancer specific survival was calculated from the time of surgery to death of colorectal cancer or last follow-up. The prognostic value of different parameters was analysed using the Kaplan-Meier method with log-rank test for comparison of groups, and Cox regression for multivariable analysis.

Results: A total of 115 patients with locally advanced T3 tumours and 20 T4 tumours were included. All patients responded to treatment and the rate of complete pathological response was 99%. The median follow-up was 42 month (12-122). Thirty-two patients died during the observation period, and 27 were cancer related deaths. The 5 year cancer specific survival rate was 79% (95% CI: 72-86%) and the overall survival rate 76% (95% CI: 69-83%).

Conclusion: Single nucleotide polymorphism analysis is a clinically attractive approach to marker analysis. The prognostic value of the EGFR Sp1-216, TS and EGF A61G genotype was investigated in rectal cancer patients treated with preoperative chemotherapy. The EGFR Sp1-216 polymorphism showed independent prognostic value in multivariate survival analysis and may have important prognostic information in this group of patients.

P.55 GENOMIC MARKERS FOR RESPONSE TO NEOADJUVANT CHEMORADIATION IN LOCALLY ADVANCED RECTAL CANCER

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Objectives: To date there is no effective method of predicting tumor response to chemoradiation in rectal cancer. We examine the role of gene expression profile as a biomarker and as potential predictor to treatment response. Furthermore differences in gene expression between healthy mucosa and tumor samples after chemoradiation were investigated.

Method: Samples from healthy rectal mucosa and tumor tissue were obtained from a total of 10 patients with locally advanced rectal cancer. Both healthy and tumor tissue samples were obtained after chemoradiation. DNA was extracted and purified selecting 28S/18S ratio >1.5 to obtain cDNA and cRNA for hybridization of microarrays included in Human WG CodeLink bioarrays. For each array, 2ug of cRNA was compared to 2ug of healthy cRNA. Significant genes were found using Significance Analysis of Microarrays (SAM).

Results: The analysis of healthy and tumor tissue after chemoradiation revealed 41 genes differentially expressed between both groups. Some of these genes were: FAT4, a cell-cell adhesion molecule. QKI, a RNA-binding protein acting as translational repressor; MAP4, a structural protein involved in the filamentous cross-bringing between microtubules and other skeletal elements; PTPLA, a member of protein tyrosine phosphoryse, which can act as anti- phosphoryase; MRGPRF, an orphan receptor, which can bind to a neuropetide and might regulate nociceptor function; GP130, a signal transducer for several cytokines.

Conclusion: Our preliminary data showed that gene expression profile identifies biologically relevant over-expressed genes related to transcription regulation in rectal cancer patients as compared to healthy volunteers. Furthermore, peripheral blood samples could represent a relevant biomarker for response to neoadjuvant chemoradiation in locally advanced rectal cancer.

P.56 MICROARRAY ANALYSES ON THE EFFECT OF CHEMORADIATION ON TISSUE GENETIC EXPRESSION IN RECTAL CANCER

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Objectives: Our preliminary results of gene expression profile identify relevant over-expressed genes in rectal cancer tissue after chemoradiation. A validation of these results and the analysis of the genes differentially expressed between responders and non responders to this therapy on the basis of tumor grade resection are being carried out.

P.57 METHYLATION TOLERANCE DUE TO O6-METHYLGUANINE DNA METHYLTRANSFERASE (MGMT) FIELD DEFECT IN THE COLONIC MUCOSA: AN INITIATING STEP IN THE DEVELOPMENT OF MISMATCH REPAIR DEFICIENT COLORECTAL CANCERS

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Objectives: O6-methylguanine-DNA methyltransferase (MGMT) removes methyl adducts from O6-guanine. Known as methylation tolerance, selection for mismatch repair (MMR)-deficient cells that are unable to initiate lethal processing of O6-methylguanine-induced mismatches in DNA is observed in vitro as a consequence of
P.58 EGFR OVER-EXPRESSION AND K-RAS ONCOGENE MUTATION IN COLORECTAL CANCER

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Objective: Epidermal growth factor receptor (EGFR) is a subtype of transmembrane receptor composed of tyrosine kinase activity and it is stimulated by epidermal growth factor (EGF) or TNF-a. The activation of EGFR receptor enhanced intracellular signal transduction, cell proliferation, and ultimately suppress apoptosis processes. K-ras is a gene, which is a 21 kDa protein molecule, located in the inner plasma membrane and involved in the mitotic signal transduction of the cell. K-ras protein is activated in response to the extracellular signals such as EGF. However, if it is mutated, K-ras protein resist to regulatory GTP activity and consequently activated without extracellular growth signals. Recently many research has investigated efficacy of new molecular agent; anti-EGF monoclonal antibody (etuximab) and revealed that it’s efficacy closely related to K-ras mutation. Henceforth, authors investigated whether EGFR over-expression is interrelated to K-ras mutation, and if so, then there is any clinical significance compared with clinicopathologic factors.

Method: From June 2008 to march 2009, at St. Mary’s hospital Seoul, we collected 192 colorectal cancer patients underwent surgical resection, and among them included 76 cases which has tested for EGFR over-expression and K-ras mutation. We retrospectively examined collected data such as EGFR over-expression status, K-ras mutation, and clinicopathologic data. EGFR expression was examined by immunohistochemical analysis. And EGFR status was considered positive when more than 10% of the tumour cells had membranous staining. K-ras mutations were analyzed by direct sequencing at codons 12 and 13 of K-ras using genomic DNA.

Results: Mean age 61.5 (range 30-87) age and male to female ratio 46:54; and according to TNM stage, 1 case is stage I, 9 cases are stage II, 35 cases are stage III and 12 cases are stage IV respectively. EGFR over-expression is observed in 50 cases out of 75 (66.7%) patients. K-ras mutation is happened in 27 cases out of 76 (35.5%). EGFR overexpression rate is closely related to K-ras mutation rate (p-value=0.041). Also EGFR over-expression is observed frequently in patients with acutes (p=0.032), mucinous adenocarcinoma and normal CEA level preoperatively are inversely related with EGFR over-expression (p=0.01, 0.017). And K-ras mutation is more frequent in cases with tumor size under 5cm (p=0.014).

Conclusion: The K-ras oncogene mutation was found in 35.5% and EGFR over-expression was found in 66.7%. And EGFR overexpression rate is closely related to K-ras mutation rate. Also K-ras oncogene mutation and EGFR over-expression are significantly interrelated with other clinicopathologic factor such as tumour size, presence of acutes and cell type. Further studies regarding prognostic value of K-ras oncogene mutation and EGFR over-expression on cancer prognosis and it’s effects on chemotherapeutic agent are warranted.

P.59 POST-OPERATIVE INFLAMMATION INCREASES PERITONEAL METASTASIS IN A MOUSE MODEL WITH AN ABDOMINAL INCISIONAL WOUND

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Objective: Post-inflammatory processes associated with the early postoperative state contribute to peritoneal metastases in patients with advanced diseases. To identify whether the wound healing response after an abdominal incision leads to increased MMP-9 activity locally, providing a favorable environment for peritoneal metastases.

Method: Post-inflammatory processes associated with the early postoperative state contribute to peritoneal metastases in patients with advanced diseases. To identify whether the wound healing response after an abdominal incision leads to increased MMP-9 activity locally, providing a favorable environment for peritoneal metastases.

Results: Post-operative inflammation increases peritoneal metastasis in a mouse model with an abdominal incisional wound. By making an incision into the abdominal wall, an inflammatory response was induced in the mouse and we observed an increased incidence of peritoneal metastasis. The inflammatory response initiated by the wound, in turn increased the proliferation of the mesothelial cells and provoked expression from the inflammatory cells, which contributed to an increase in peritoneal peritoneal metastases.

Conclusion: The wound healing process increases pro-inflammatory cytokines and the number of inflammatory cells in the peritoneum. This leads to an increase in the level of pro- MMP9 protein. We hypothesize the increased pro-MMP9 protein plays a key role in the growth and progression of cancer cells associated with peritoneal metastases.

P.60 KERATIN 7 EXPRESSION IN COLORECTAL CANCER - FREAK OF NATURE OR SIGNIFICANT FINDING?

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Objectives: Non-neoplastic colorectal mucosa as well as colorectal adenoma and/or carcinoma generally lack expression of keratin 7 (K7). Recent evidence, however, indicates that some colorectal tumours acquire K7 expression during neoplastic process. Our study aimed to assess the prevalence of K7 expression in colorectal cancer and to correlate findings with clinicopathologic parameters as well as patient outcome.

Method: 370 patients were evaluated for K7 expression by immunohistochemistry using a tissue microarray technique. Follow-up data were available for 340 (92%) patients. Median follow-up was 59 months (mean 63 months, range 0-180). At the time of last follow-up, 165 (48%) patients showed no evidence of disease. Progressive disease was observed in 141 (41%) patients including 117 (34%) patients who died from cancer and 11 (3%) patients who currently are alive with metastatic disease. K7 expression was semiquantitatively scored as either focal (<10%), moderate (10-50%) or extensive (>50%). K7 expression was related to various clinicopathological parameters as well as progression-free and cancer-specific survival, respectively.

Results: 32 out of 370 (9%) tumour samples were immunoreactive for K7, with 5 cases showing extensive, 4 moderate and 23 focal expression, respectively. K7 immunostaining prevailed in single cells and small cell clusters at the invasion front and was significantly associated with poor tumour differentiation. Thus, 18 out of 119 (16%) positive high grade (G3/G4) compared to 26 out of 251 (10%) low grade cancers showed K7 expression (p=0.01). In addition, K7 expression was associated with the amount of tumour budding. Tho. 20 out of 158 (13%) tumours with high grade budding (budding foci at 50% of tumour section) showed K7 expression compared with 12 out of 212 (6%) tumours with low grade budding (p=0.02). Disease progression occurred in 15 out of 29 (52%) patients with K7-positive tumours and 126 out of 311 (40%) patients with K7-negative tumours (p=0.19, log-rank test). Actuarial 5-year progression-free survival rates for patients with K7-positive and patients with K7-negative cancers were 43% and 60%, respectively. In addition, 14 (29%) patients with K7-positive tumours and 103 (33%) with K7-negative tumours died of disease (p=0.06, log-rank test). Actuarial 5-year cancer-specific survival rates for patients with K7-positive and patients with K7-negative tumours were 51% and 66%, respectively.

Conclusion: K7 expression is rarely observed in colorectal cancer and is, if present, usually found only in a minority of tumour cells. Remarkably, K7 positive tumour cells cluster at the invasion front, correlating with the amount of tumour budding. Our data thus indicate that changes in the cytoskeleton, especially in intermediate filament composition, occur during the process of epithelial-mesenchymal transition. Further studies assessing the prognostic value of K7 expression are warranted.

P.61 PILOT STUDY ON LAT-1 EXPRESSION AND 4-FMP PET IMAGING IN COLORECTAL CANCER

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Purpose: LAT1, a neutral L-type amino acid transporter, and its transmembrane component CD98 are known highly expressed in gliomas. Therefore, LAT1 is recently suggested as a novel molecular target in brain tumors that may affect the outcome of conventional chemo and radiotherapy. In this study, we examined the expression of LAT1 and CD98 in colon cancer using real time RT-PCR and immunohistochemistry (IHC). Next, we evaluated the feasibility of using [18F]-4-methylphenylalanine (4-FMP), a radiolabelled amino acid, as PET tracer.
The p53 homologue p73 acts on the transcription of p53-responsive genes, thereby inhibiting cell growth. The use of an alternative promoter in the TP73 gene gives rise to an N-terminally truncated isoform, Anp73, lacking the transcription domain of the full length protein, Tap73. As a result of alternative splicing there are also several C-terminal isoforms, β, etc. The full length isoforms of p73 are generally believed to be pro-apoptotic, and Anp73 anti-apoptotic. In this study, we overexpressed Anp73 β in colon cancer cells HCT116p53+/+ and HCT116p53-/-, and further treated the cells with the DNA-damaging drug cisplatin. Protein expression was determined using Western blot. Cell viability was determined with the XTT assay, clonogenic assays were performed, and apoptosis was measured by means of M30-ApoptoSense ELISA and DAPI staining. We found that overexpressed Anp73 β was decreased after the cisplatin treatment in a dose dependent manner, and Tap73 and p53 were also upregulated. The p53 was increased in the cells overexpressing the Anp73 β. As expected, cisplatin decreased cell viability, clonogenic potential and increased apoptosis in both cell lines, but to a lesser extent in HCT116p53-/- than in HCT116p53+/+. Further, viability was significantly increased in Anp73 β -vector transfected cells compared to mock vector transfected cells, both HCT116p53+/+ (p=0.005) and HCT116p53-/- (p=0.01). We did not find that Anp73 β overexpression significantly influenced sensitivity to cisplatin.

Conclusion: Np73 β is involved in anti-apoptotic process, a forced overexpression of Anp73 β increases viability in colon cancer cell line HCT116, and further that cisplatin treatment induces the degradation of Anp73 β in a dose dependent manner.

P.06 ASSESSMENT OF ATTITUDES OF LIVER SURGEONS TO SYNCHRONOUS RESECTION OF COLORECTAL CANCER AND LIVER METASTASES

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Introduction: The management of patients with primary colorectal tumour and synchronous liver metastases is controversial. This study was designed to assess the attitudes of the United Kingdom liver surgeons to the management of primary colorectal tumours and synchronous liver metastases.

Method: An electronic survey of 52 Association of Upper Gastrointestinal Surgeons (AUGIS) members was performed using a standard questionnaire.

Results: 22 of the 52 (42%) consultant surgeons’ responded. 83% of them had been involved in synchronous resection in the past. A majority (83%) recognised that there is still a significant role for synchronous resections although many colorectal resections are enhanced recovery programme. 78% stated that there is a role for open synchronous resection given that there is a trend towards laparoscopic resection of the primary. In fact, a majority (74%) believed that synchronous resection of the primary bowel tumour and secondary liver metastases could be performed laparoscopically. There was an increasing enthusiasm amongst liver surgeons (96%) to participate in synchronous resection in the future. The possible advantages of synchronous resections were: decrease in overall length of hospital stay (82%); decreased cost (83%); decreased patient anxiety (73%). The major concerns that might stop them from performing synchronous resections were: an excessive overall physiological stress (93%) and a significant rate of anastomotic leakage (54%); an inability to observe the tumour biology in a staged manner (33%). Eight clinical scenarios involving colorectal surgery and liver resection of varying complexity were also questioned and reported on.

Conclusion: Although a significant number of concerns remain amongst liver surgeons regarding synchronous resections, a majority of them felt that synchronous resections could be offered to an appropriately selected group of patients on a routine basis.

P.06 ASSESSMENT OF ATTITUDES OF COLORECTAL SURGEONS TO SYNCHRONOUS RESECTION OF COLORECTAL CANCER AND LIVER METASTASES

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Method: An electronic survey was sent to the Consultant members of the Association of Coloproctology of Great Britain and Ireland (ACPGBI). The survey was sent by email and a reminder sent six weeks later.

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Results: 424 consultant members of the ACPGBI were identified. Responses were obtained from 133 of the 424 (31%). 34% of the responders work in a Center where liver surgery is practised. 95% believe that liver metastases are a potentially curable problem. 49% had previously referred patients for synchronous resection. The factors that would dissuade a colorectal consultant from referring a patient for possible liver resection were:

- presence of peritoneal metastases (97%)
- the overall fitness of patient (89%)%
- pulmonary metastases (54.9%)
- number of affected healthy liver segments (46%)
- liver metastases of more than a certain number (22%)
- bilobar liver metastases (21%)
- liver metastases of more than a certain size (8%).

A majority (67%) felt that there remained a role for synchronous resection in the era of:

- a) an enhanced recovery programme and b) laparoscopic surgery.

A majority (79%) stated that they would consider referral for synchronous resection in the future. The potential major benefits associated with synchronous resection were:

- decrease in overall length of hospital stay (73%)
- decreased patient anxiety (62%)
- the opportunity to start chemotherapy earlier (61%)
- decreased total cost (57%)

The major concerns highlighted that would dissuade referral for possible synchronous resection were:

- excessive overall physiological insult (48%)
- an inability to observe the tumour biology in a staged manner (44%)
- perceived greater risk of anastomotic leakage (24%).

Conclusion: The majority of the responders considered synchronous resection in what they considered appropriately selected patients. There seemed to be enthusiasm to make referrals in selected cases where this hadn’t happened before. Overall physiological insult and an inability to observe the tumour biology in a staged manner were the main identified risks associated with the procedure.

P.67 PSEUDOMYXOMA PERITONEI OF THE APPENDICULAR ORIGIN: THE ROLE OF FLUORESCENT LAPAROSCOPY AND INTRAPERITONEAL PHOTODYNAMIC THERAPY IN THE COMBINATION WITH CYTOREDUCTIVE SURGERY

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Background: Pseudomyxoma peritonei (PMP) is a rare clinical syndrome including progressive intraperitoneal accumulation of mucous and mucinous implants, usually originates from the mucinous tumors of appendix or ovaries. The traditional approach to PMP is based on the surgical cytoreduction combined with intraperitoneal or systemic chemotherapy.

Materials and method: A total of 9 PMP patients (7 men and 2 women), that underwent cytoreductive surgery in the combination with photodynamic therapy (PDT) between 2006 and 2009 were included in this study. The mean age of patients was 51,4±10,5 years (range 25-72). The primary site of the pseudomyxoma was the appendix. The mean PCI was 17,6±9,8 (range 4-35). 6 (67%) patients were identified with disseminated peritoneal adenomucinous (DPAM), 3 (33%) patients - with peritoneal mucinous carcinomatosis (PMCA). Diagnostic fluorescent laparoscopy with Karl Storz D-light system and «Alasens» photosensitiser was performed in 8 patients. All patients underwent subtotal partial peritonectomy, appendectomy, subtotal omentectomy, intraperitoneal PDT with «Photogem» photosensitiser. Additional right hemicolectomy was performed in 3 patients with PMCA (well differentiated mucinous adenocarcinoma of appendix). 8 patients are available for analysis of long term results in a median follow-up time of 20 months (range 10 - 40).

Results: Cytoreduction was considered CO1 - in 1 (11,1%) patients, CC1 - in 5 (55,6%), CC2 - in 3 (33,3%). Postoperative wound complications occurred in 1 (8,3%) patient. There was no PDT-associated toxicity as well as no postoperative mortality. Adjuvant chemotherapy (FOLFOX4) was performed in all 3 patients with PMCA. Among the traced 8 patients all are still alive, 6 (75%) of them are free of disease. Recurrence occurred in 2 (25%) patients after CC2 cytoreduction. Both of them underwent the second procedure: fluorescent laparoscopy with laparoscopic PDT (Photogem) - in 1 patient, laparotomy with CC1 cytoreduction and intraperitoneal PDT (Photogem) - in 1.

Conclusion: Cytoreductive surgery in the combination with intraperitoneal photodynamic therapy is a feasible treatment strategy for PMP of the appendicular origin. Optimal cytoreduction is the most important component of treatment of peritoneal pseudomyxoma patients.

P.68 THE ROLE OF TOTAL AND POSTERIOR PELVIC EXENTERATION FOR TREATMENT OF LOCALLY ADVANCED PRIMARY AND RECURRENT RECTAL CANCER: EXPERIENCE OF 30 CASES

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Background: Currently, about 15-30% of primary rectal cancer patients experiencing with the locally advanced (T4) tumors. On another hand, local recurrence after curative surgery for primary rectal cancer occurs in 4 to 20% of cases. For locally advanced rectal tumors (primary as well as recurrent), which involve other pelvic organs, the extended surgery including pelvic exenteration seems to be necessary component of radical treatment.

Materials and method: Overall 30 patients with locally advanced rectal tumors were included. 13 pts (5 men, 8 women) were presented with primary locally advanced rectal cancer (Group A), 17 pts (7 men, 10 women) - with recurrent rectal tumors (Group B). The mean age of patients was 52,3±14,4 years (range 28-78) in the Group A, and 54,8±9,2 years (range 32-70) in the Group B.

All patients underwent subtotal parietal peritonectomy, appendectomy, subtotal omentectomy, intraperitoneal PDT, abdominal lymphadenectomy, and pelvic exenteration. In Group A patients with synchronous resection were: - excessive overall physiological insult (48%) - the opportunity to start chemotherapy earlier (61%) - decrease in overall length of hospital stay (73%) - perceived greater risk of anastomotic leakage (24%).

Conclusion: Surgical cytoreduction and intraperitoneal PDT with «Photogem» photosensitiser is a feasible treatment strategy for PMP of the appendicular origin. Optimal cytoreduction is the most important component of treatment of peritoneal pseudomyxoma patients.

P.68 Table 1.

<table>
<thead>
<tr>
<th>All pts.</th>
<th>TFE</th>
<th>PPE</th>
<th>Mean operative time, min</th>
<th>Mean blood loss, ml</th>
<th>R0 resection</th>
<th>R1 resection</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary rectal cancer</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>419.6±121.4 (270-665)</td>
<td>2108.3 (300-6500)</td>
<td>10 (77%)</td>
<td>3 (23%)</td>
<td>6 (46,1%)</td>
</tr>
<tr>
<td>Recurrent rectal cancer</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>428.8±127.2 (240-680)</td>
<td>4887.5 (708-12000)</td>
<td>13 (76,4%)</td>
<td>4 (23,6%)</td>
<td>10 (58,8%)</td>
</tr>
</tbody>
</table>

April 2010
Method and patients: main point of polyradiomodification programme created in 2004 is reinforcement of tumoral necrosis (TN) by use of interstitial hyperthermia (HT) (superhigh frequency, SHF) using the ‘Yalik’ and ‘Yahtia-4’ device, given on day 3, 4 and 5 of radiotherapy (frequency 460 MHz, exposure 60 min, temperature inside tumor 43.5-44.0°C), just before irradiation. And METRONIDAZOLE (MZ) (10 gr/m2) in a form of hydrogel on basis of biopolymer Sodium alginate (KOLEGEL) administrate intrarectally on days 5 and 5 of RT, exposure 5 hrs, prior to RT. And patients also received METRONIDAZOLE (XELODA) orally in daily dose of 1.5 gr/m2, twice a day, all days of RT. We use 2 radiomodifier of hypoxic tumor cell - local Hyperthermia (HT) which add chemosensibilisation effect achieved by adding to neoadjuvant treatment scheme oral METRONIDAZOLE (XELODA). This optimistic results evidence competence of use of polyradiomodification programme in combined treatment of rectal cancer and broadening indication to sphincter-saving surgery for rectal cancer of middle and low third localization.

P.71 DOES POSTOPERATIVE ADJUVANT FLUOROPYRIMIDINE-BASED CHEMOTHERAPY PROVIDE A BENEFIT FOR PATIENTS WITH RESECTABLE RECTAL CANCER WHO HAVE ALREADY RECEIVED NEOADJUVANT RADIO(CHEMO)THERAPY? A SYSTEMATIC REVIEW OF RANDOMIZED TRIALS

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We conducted a systematic review of randomized controlled trials (RCTs) assessing postoperative adjuvant fluoropyrimidine-based chemotherapy (FAC/FOLFOX) in patients with resectable rectal cancer who have previously undergone neoadjuvant radiotherapy. A total of 5427 patients were included. The most recent data cut-off was October 2008. A meta-analysis showed that postoperative fluoropyrimidine chemotherapy was associated with a significant improvement in disease-free survival (DFS) and no increase in toxicity.

Conclusion: Postoperative fluoropyrimidine chemotherapy provides a survival benefit for patients with resectable rectal cancer who have previously undergone neoadjuvant radiotherapy.
combined with resection. 51 patients (85%) in the RFA+CT arm received CT compared to all 59 in the CT arm. The median number of chemotherapy cycles for patients who received CT was 10 in the presacral area. Toxicity profiles for CT were comparable between both arms. Post-operative complications were observed in 10 cases after RFA (33%) and in 9 cases (33%) after RFA + resection. Major complications were cardiac failure (5), hemorrhage (2) and infection (6), and patients needed re-operation. Minor complications were fever (12) and fatigue (6). There was one post-operative death (1.8%). One year PFS is 39.35% (95% CI 26.78-51.67) in the CT arm versus 60.06% (46.24-71.40) in the RFA+CT arm (overall log-rank P=0.0267). At present interim analysis, median PFS is 10 mo in the CT arm versus 16.8 mo in the RFA + CT arm. The number of patients with local recurrence at the RFA site only was 5.

Conclusion: This is the first study that prospectively investigates the efficacy of RFA in combination with CT. In pts with unresectable colorectal liver metastases RFA + CT is safe and improves PFS compared to CT alone.+

P.73 WHAT IS THE ORIGIN OF THE PRESACRAL LOCAL RECURRENT IN RECITAL CANCER? - AN ANATOMIC STUDY OF THE LATERAL LYMPH NODES IN HUMAN FETUSES

1Catharina-hospital, Eindhoven, The Netherlands; 2Amsterdam University Medical Center, Department of Anatomy, Amsterdam, The Netherlands; 3Leiden University Medical Center, Department of Anatomy, Leiden, The Netherlands; 4Leiden University Medical Center, Department of Surgery, Leiden, The Netherlands; 5Catharina-hospital, Department of Surgery, Eindhoven, The Netherlands

Objectives: In various studies about patterns of local recurrence after primary rectal cancer treatment, it was shown that the presacral subsite is the main site of local relapse, even after radical resections. As in one study after a bilateral lymph node dissection less presacral local recurrences developed than after a unilateral lymph node dissection, it is our hypothesis the lateral lymph nodes might play a role in local recurrence genesis. The objective of this study is to obtain detailed anatomical knowledge about the lateral lymph nodes, in order to learn whether these might play a role in presacral local recurrence genesis after total mesorectal excision without lateral lymph node dissection.

Method: Ten serially sectioned human fetal pelvises were studied at high magnification and a 3D reconstruction of the fetal pelvis was made.

Results: In the histologic sections and in the 3D reconstruction (Figure) it was shown that the lateral lymph node tissue comprises a major volume in the pelvis. There are no lymph nodes located in presacral area. Connections between the mesorectal and extra-mesorectal lymphatic system exist in all fetal pelvis, located below the peritoneal reflection on the anterolateral side of the fetal rectum. In this site also middle rectal vessels pass to and from the mesorectum and the branches of the autonomic nerve system bridge to innervate the rectal wall.

Conclusion: Our hypothesis is that during the mobilisation of the rectum during the surgical excision procedure, lymph fluid and tumor cells flow into the lateral lymph node system. The findings of this study, that there are connections between the mesorectal and extra-mesorectal lymphatic system, support the hypothesis that tumor recurrence might occur from these lateral lymph nodes. As these are left behind in standard total mesorectal excision and partly damaged during sharp dissection of the lateral ligament, one would expect that the basins start leaking after the procedure. The lymph fluid, collected presacrally in a seroma, might rise to local tumor recurrence. This study gives more insight in the anatomy of the lateral lymph nodes, but still cannot prove the hypothesis. Currently further studies are conducted to elucidate presacral local recurrence genesis. More attention should be paid to the role of the lateral lymph nodes in the development of local recurrence in rectal cancer, especially if with intensity modulated radiation therapy (IMRT) targets have to be decided. Reconstruction of the pelvis prepared by immunohistochemically stained serial sections of a human fetus. Structures: rectum covered by mesorectum (light blue), peritoneal reflection (orange), iliac arteries (red), iliac veins (dark blue), lateral lymph nodes (yellow) and autonomic nerve plexus (green).

P.74 DELAYED COLO-ANAL AnastomOsis FOR LOWER THIRD CANCER

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Lyon, France

Background: Delayed coloanal anastomosis (DCAA) is an alternative to the J-pouch coloanal anastomosis. It avoids the need of a diverting stoma, only requires one hospital stay and is feasible by laparoscopy.

Objective: The aim of this study was to assess oncologic and functional outcomes of proctectomy and total mesorectal excision with DCAA for lower third rectal cancer and to compare results of laparoscopic approach versus open surgery.

Method: From 1988 to 2007, 92 patients underwent rectal resection for low rectal cancer with DCAA without diverting stoma. 45 patients benefited of a laparoscopic approach (Group A) and 47 open surgery (Group B).

Results: The overall operative mortality and morbidity rates were 1.1% and 40% respectively, while the surgical mortality and the reoperation rates were 15% and 8.7%, respectively. Anastomatic leak occurred in 6.5% of patients. In group A, conversion rate was 20% and only 3 patients required suprapubic incision for specimen extraction. Mean follow-up was 71 months. Curative resection (R0) was performed in 95 patients (98%). The 5-year actuarial global survival, disease-free survival and local recurrence rates were 84%, 72% and 7% respectively. Function was considered good in 82% at 1 year. There were no differences in oncologic and functional outcomes between the two groups.

Conclusion: There is no difference in oncologic and functional outcomes between laparoscopic and open surgery for low rectal cancer. DCAA is a safe procedure and is perfectly suited to a laparoscopic approach. It avoids the need of a diverting stoma and requires only one hospital stay.

P.76 DOES RECTAL CANCER REGRESSION TO MINIMAL MICROSCOPIC DISEASE AFTER PREOPERATIVE CHEMORADIATION HAVE A PROGNOSTIC VALUE?

K. Bujko1, M.Kolodziejczyk2, A. Nasierowska-Guttmejer3, E. Chmielik4, A. Wojna5, M. Cwalinski6, W. Michalski7
1Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; 2Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; 3Department of Pathology, Maria Sklodowska-Curie Memorial Cancer Center, Gliwice, Poland; 4Department of Pathology, Maria Sklodowska-Curie Memorial Cancer Center, Gliwice, Poland; 5Department of Colorectal Cancer, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; 6Department of Biostatistics, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland

Objectives: The pathologic complete response (pCR) in primary tumour after preoperative chemoradiation predicts low risk of mesorectal nodal disease and excellent disease-free survival. The objective of this analysis is to find out whether regression to minimal microscopic disease does have similar prognostic value.

Method: Of the 143 patients who received preoperative chemoradiotherapy in the frame of the Polish trial (Br J Surg 2006, 93:1215), 132 patients had assessment of tumour regression grading (TRG) in the primary tumour. TRG0 (pCR), minimal microscopic disease (few cancer foci seen in less than 10% of slices, TRG1), moderate regression (TRG2), and poor regression (TRG3) was recorded in 17%, 30%, 30%, and 23% of patients, respectively.

Results: The rates of ypN-plus category for TRG0, TRG1, TRG2, and TRG3 groups were 5%, 23%, 45%, and 48%, respectively, P=0.001. When ypT category and TRG were evaluated by the logistic regression analysis, only ypT category remained significant for independent prediction of the risk of nodal disease, p=0.001. Disease-free survival (DFS) analysis demonstrated better prognosis for the TRG0 group compared to the remaining patients, p=0.013. When patients with persistent disease where analyzed separately, TRG had no prognostic value; the 5-year DFS rates for TRG1, TRG2, and TRG3 groups were 62%, 69% confidence interval, 46%-79%, 54% (38%-70%), and 45% (25%-65%), respectively, P=0.34.

Conclusion: TRG1 compared to TRG2-3 had no prognostic value for the incidence of nodal disease and for DFS. This suggests that the diagnosis of TRG1 should not influence the decision about further treatment.
P.77 THE USE OF THE CELL SAVER IN RECTAL CANCER SURGERY IS SAFE

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1Catharina-hospital Eindhoven, Eindhoven, The Netherlands; 2Academic Medical Center, Department of Experimental Surgery, Amsterdam, The Netherlands; 3Eindhoven Cancer Registry, Comprehensive Cancer Center South, Eindhoven, The Netherlands

Objectives: In non-malignant surgery with substantial blood loss, preservation techniques for the patient’s own blood have become accepted. The recirculation of blood shed from the tumour bed during cancer surgery has not been adopted widely for fear of introducing viable tumour cells, which may give rise to metastases. However, fresh autologous blood is superior with regard to suppression of the immune system, but also with regard of its oxygen binding and more specifically lower affinity to oxygen molecules, which results better tissue oxygenation. In this study we present our results of using the cell saver as a standard procedure in surgery for advanced and locally recurrent rectal cancer.

Method: From 1994 until December 2006, data on 290 patients who have been treated for locally advanced rectal cancer was collected prospectively. Because of the complexity of the surgery, blood loss was more than 2.5 litres in more than half of the patients. For more than ten years, the cell saver was used to collect, filter, wash and return the patient’s erythrocytes. In case of contamination by stool, or pus, ICS blood was not returned to the patient. Four quarters representing the volume of blood loss were created. (Q1 less than 1385 ml (n=69), Q2 1385 up to 2500 ml (n=76), Q3 2500 up to 4650 ml (n=62), Q4 more than 4650 ml (n=69).

Results: Cancer specific 5-year survival for patients in whom the cell saver was used (n=151) per quartile blood volume compared to those without cell saving (n=125) were 74%, 85%, 78%, 76% and 73%, 68%, 60%, 30% respectively (p=0.042 in Q3 and p=0.004 in Q4, overall p=0.002). The percentages for metastasis free survival were 63%, 81%, 65%, 69% and 77%, 71%, 71%, and 37% respectively (p=0.038 for Q4, overall n.s.) (table 1). Other significant variables for oncological outcome were: free circumferential margin, lymph node status, the use of neoadjuvant chemotherapy compared to radiotherapy alone and the use of adjuvant chemotherapy.

Conclusion: Modelling of multivariate analysis and stratification for all tumour variables did never show a negative outcome for the use of the cell saver. In all models the trend was not returned to the patient. Four quarters representing the volume of blood loss were created. (Q1 less than 1385 ml (n=69), Q2 1385 up to 2500 ml (n=76), Q3 2500 up to 4650 ml (n=62), Q4 more than 4650 ml (n=69).

Table 1. Results Table

<table>
<thead>
<tr>
<th>Blood loss (ml)</th>
<th>Cell saver (n = 151)</th>
<th>No cell saver (n = 125)</th>
<th>p-value</th>
<th>Cell saver (n = 151)</th>
<th>No cell saver (n = 125)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Q1 (&lt; 1385)</td>
<td>74</td>
<td>73</td>
<td>n.s.</td>
<td>65</td>
<td>77</td>
<td>n.s.</td>
</tr>
<tr>
<td>Q2 (1385 – 2500)</td>
<td>85</td>
<td>68</td>
<td>n.s.</td>
<td>81</td>
<td>71</td>
<td>n.s.</td>
</tr>
<tr>
<td>Q3 (2500 – 4650)</td>
<td>78</td>
<td>60</td>
<td>.042</td>
<td>65</td>
<td>71</td>
<td>n.s.</td>
</tr>
<tr>
<td>Q4 (&gt; 4650)</td>
<td>76</td>
<td>30</td>
<td>.012</td>
<td>69</td>
<td>37</td>
<td>.038</td>
</tr>
</tbody>
</table>

Development: In order to avoid prolonged stay on the Intensive Care Unit and to avoid re-operation a device was developed that can be positioned in the pelvic cavity, and which controls bleeding and can be removed without re-operation. Together with the Faculty of Industrial Development of the Technical University Leiden a multi-chamber balloon was designed, based on 3D-reconstruction data, derived from MRI-images of male and female rectal cancer patients. The shape consistency was realised by using three separate chambers, which also have the advantage that, when inflated, the balloon would fixate itself in the pelvic cavity. First clinical results. Five of the prototypes have been used to see if the fit in the pelvic cavity was good, and to see whether the balloon when insufflated would retain in the pelvic cavity. Typically the balloon pressure in the balloons would not exceed 30 cm of water. Subsequently, five balloons were used in clinical situations. The patients all had blood loss exceeding 5 litres, two after locally recurrent rectal cancer, one after extended endometroid cancer, and two after locally advanced rectal cancer with wide extra-anatomical resection. In four out of five patients the balloon completely stopped the bleeding, even in the presence of coagulation disturbances. The patients could leave the ICU the day after the operation. The pressure on the balloons, which was typically in the area of 20 tot 30 centimetres could be relieved on the first day, no re-bleeding did occur and on the second day the balloons were totally collapsed by applying negative pressure on the chambers. On the third day they could be removed like a drain. This all happened in the surgical wound without the necessity of any anaesthesia or pain medication. The fifth patient was not controlled by the balloon, and to be re-operated on the same day.

Conclusion: The first prototypes of a multi-chamber haemostatic rectal cavity balloon were used in clinical situations and did perform well. The number of ICU-days was significantly reduced, and re-operation was not necessary in most cases.

Figure 1. Cancer Specific Survival All Variables.

Table 1. Results Table

<table>
<thead>
<tr>
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</tbody>
</table>
P.79 PRE- AND POST-OPERATIVE STAGING IN THE MANAGEMENT OF COLORECTAL CANCER. WHAT LESSONS CAN WE LEARN?

H. West, D. Mathur, Saleem Jonnalagadda, Sandeep Taneja, Leone Walker
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Objectives: In the UK the 50% five year survival rate from colorectal cancer is less than that in Western Europe and the USA. The differences may be due to late presentation, poorer access to diagnostic investigations or lifestyle. The National Bowel Cancer Audit Project building on the existing audit of the Association of Coloproctology has identified that hospitals need to provide better data on: circumferential resection margin involvement, local staging, excision of lymph nodes, MDT discussions and ASA grade. Comparative data is essential for quality of clinical care and patient outcomes. This was a retrospective study on patients undergoing surgery for colorectal cancer with curative intent. Pre- and post-operative staging was compared together with details of surgical procedures. The overall objective was to improve accuracy of staging, inform management and improve long-term survival rates.

Method: Data was collected from 2006-2008 on a total of 67 patients undergoing surgery for colorectal cancer who had pre- and post-operative staging. Pre-operative investigations such as colonoscopy or flexible sigmoidoscopy with biopsy and computed tomography (CT) scans of the chest, abdomen and pelvis were compared with findings at surgery including site of tumour, stage and grade of colorectal cancer and lymph node sampling. Pre- and post-operative chemotherapy and radiotherapy were also recorded. Patients with rectal carcinoma had MRI scans.

Results: Age at surgery ranged from 45-85 years with 39 male and 28 female patients. There was 100% correlation between site of tumour on pre-operative flexible sigmoidoscopy/ colonoscopy and CT and at surgery and between pre-operative biopsy and tumour type at surgery. Most were moderately differentiated adenocarcinomas and Dukes grades were recorded. 91% of patients had negative resection margins. 25.4% had extramural vascular invasion and 31.3% had less than 12 lymph nodes sampled. When comparing pre-operative CT staging and post-operative histology: in 85.3% of patients there was a direct correlation with the presence of metastases (Figure 1); in 41.7% of patients a positive correlation for tumour size (Figure 2) and in 54.2% a positive correlation for nodal involvement. Post-operative follow-up, treatment and survival were recorded.

Conclusions: Pre-operative staging was accurate for ruling out metastases but gave variable results for tumour size and nodal involvement. Pre-operative colonoscopy and biopsy were accurate in diagnosing the site and type of tumour and pre-operative CT was accurate in diagnosing tumour site. Decisions for pre- and post-operative treatment were more accurate as they were based on CT and histology findings. Recommendations were for all patients to have pre-operative staging with CT and biopsy and to aim to sample at least 12 lymph nodes.

P.80 IMPROVEMENT OF SURGERY AND USE OF RADIOCHEMOTHERAPY IMPROVED OUTCOME OF ABDOMINO-PERINEAL RESECTION FOR RECTAL CANCER SIGNIFICANTLY

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Introduction: Since 1994 our hospital is a referral center for locally advanced rectal cancer. Especially in patients undergoing abdomino-perineal resection (APR) a major concern is to realize a radical resection with free circumferential margins (CRM). During the existence of this center, both surgical technique and change in neoadjuvant treatment took place to realize this objective. Since 1994 the pathology lab uses Quirke’s transversal slice technique to evaluate the CRM. All patients had preoperative MRI imaging of the pelvis.

Patients and method: Since 1994, 443 patients were referred to be treated for unmetastasized T3 tumors in which there was no visible margin between the tumour boarder and the mesorectal fascia and T4 tumors. 279 male and 164 female patients with a median age of 63 were treated. Since 2000 neoadjuvant treatment has changed from radiotherapy alone to radiochemotherapy. In 243 patients an APR was performed.

Results: In three time periods: 1994-2000 (n=36) ; 2001 - 2004 (n=95) and 2005-2009 (n=112), the radical resection rate in APR patients improved from 33%, 17% to 7% respectively (p< 0.0001). The three year cancer specific survival rate improved from 72%, 83% to 88%. Whereas, the three year local recurrence rate decreased from 19%, 13 to 4%. In multivariate analysis, Radicality of resection (p=0.004) and use of neoadjuvant radiochemotherapy compared to radiotherapy alone (p=0.021) were the most significant predictors of outcome independent from the observed time periods.

Conclusion: The radical resection rate reflects the surgical technique, which consists of an anatomical extralevatoric approach. Most patients were operated in prone position with adjustable stirrups for the legs. Patients were only turned from prone to supine position in case a sacrum resection was necessary. In some patients having had cancerous fistula in the perineum or very distant ano-rectal carcinomas a wider perineal...
excision was performed. In these cases a vertical rectus abdominis muscle-cutaneous flap was used to close the perineal gap. However, in most APR patients skin and ischiorectal fat were spared, and primary closure was possible. No meshes or musculo-fascial flaps were used for primary closure. In the early years neoadjuvant treatment consisted of long course radiotherapy 1.8 Gy fractions up to 90.4 Gy. Since 1998 incidentally patients were treated with the Mayo Scheme consisting of bolus injections SFU combined with leucovorin in week 1 and 5 of the radiotherapy period. Since 2000, this scheme became the preferred standard for these patients. Later, since 2003 combination radiochemotherapy of SFU and oxaliplatin was introduced. In the last period most patients received single modality radiochemotherapy with capecitabine.

The fact that many colorectal surgeons have cooperated in identifying there advanced combination radiochemotherapy of 5FU and oxaliplatin was introduced. In the last this scheme became the preferred standard for these patients. Later, since 2003 INC accession patients were treated with the Mayo Scheme consisting of bolus injections SFU in week 1 and 5 of the radiotherapy period. Since 2000, this scheme became the preferred standard for these patients. Later, since 2003 combination radiochemotherapy of SFU and oxaliplatin was introduced. In the last period most patients received single modality radiochemotherapy with capecitabine.

Contribution: We found variable degree of hepatic injury after chemotherapy for resectable hepatic metastases of colorectal primary. Metastasectomy, however, could safely be performed even in patients with severe degree of hepatitis. Our results warranted further accumulation of experiences of PCM for resectable hepatic metastases.

Figure 1. Local recurrence rate in different time periods

P.81 CHEMOTHERAPY INDUCED HEPATIC INJURY DOES NOT AFFECT OUTCOMES FOLLOWING HEPATIC METASTASECTOMY

K.W. Suh
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Background and purpose: For the resectable hepatic metastases from colorectal cancer, it is still controversial whether preoperative chemotherapy and hepatic metastasectomy (PCM) is superior to metastasectomy and postoperative chemotherapy (MPC). One of the major drawbacks of PCM is possible hepatic injury by chemotherapeutic agents and following postoperative complications. The objective of this study was to identify if there is any correlation between degree of hepatic injury after PCM and surgical outcomes.

Method: Sixty one consecutive patients with hepatic metastases of colorectal primary who underwent hepatic metastasectomy of curative intention from 2000 to 2008 were studied. Metastasectomy was performed by same surgeon. Since 2000 to 2004, our policy of treatment for resectable hepatic metastases had been MPC (N=21) and since 2004 when oxaliplatin or irinotecan based chemotherapy was adapted, policy has changed to PCM (N=40). We compared liver function profiles before metastasectomy, histologic findings of normal liver around the metastases, surgical complications, and mortality between 2 groups. In PCM groups, 15 were treated with irinotecan based chemotherapy and 25 with oxaliplatin based chemotherapy.

Results: Demographic comparison between two groups did not show significant difference. Types of hepatic resection also were similar in both groups. In PCM group, hepatic functional profiles showed significant aggravation in PCM group. All of the liver parenchymes around the metastatic area showed various degree of hepatic injuries such as sinusoidal dilatation, steatohepatitis, and steatosis. Severe hepatic injuries, such as steatosis more than 30% and/or grade 3 sinusoidal dilatation, and/or severe steatohepatitis (Kleiner score >4) were found in 14 patients (35.0%). The degree and pattern of hepatic injury did not vary with type of chemotherapy. In MPC group, histologic evidences of hepatic injury were not found. However, rate and type of postoperative complications, perioperative liver function change, and hospital stay were similar in both groups. There was no postoperative mortality in both groups.

Conclusion: We found variable degree of hepatic injury after chemotherapy for resectable hepatic metastases of colorectal primary. Metastasectomy, however, could safely be performed even in patients with severe degree of hepatitis. Our results warranted further accumulation of experiences of PCM for resectable hepatic metastases.

P.82 PHASE II STUDY OF PREOPERATIVE HELICAL TOMOTHERAPY FOR RECTAL CANCER

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Purpose: Preoperative radiotherapy is standard of care for locally advanced rectal cancer. However, adding concomitant chemotherapy to preoperative radiotherapy does not improve survival or the incidence of distant metastasis, and is associated with considerable grade 3+ toxic effects. The aim of this study is to explore the efficacy and toxicity profile of helical tomotherapy in the preoperative treatment of rectal cancer.

Patients and method: This interim analysis reports the first 100 patients. A dose of 46 Gy, in daily fractions of 2 Gy, was delivered to the presacral space and the perineum if an abdominopерineal resection was deemed necessary. No concomitant chemotherapy was administered, but the dose of radiation was increased by a simultaneous integrated boost to 55.2 Gy, when the circumferential resection margin (CRM) was less than 2 mm. The response was determined by measuring the metabolic tumor volume prior to and five weeks after the end of radiotherapy by FDG-PET.

Results: 47 patients presented with a T2 or good T3 tumor (CRM ≤ 2 mm) and entered the no boost group, 53 patients presented with a bad T3 (CRM < 2mm) or T4 tumor on MRI and entered the boost group. One patient, in the no-boost group, developed grade 3 enteritis. No other grade 3+ acute toxicities were observed. 14, 10, 26 and 1 patient developed acute grade 2 gastrointestinal, urinary, dermatologic and gynecologic toxic effects respectively. The mean decrease in metabolic volume was 61 ± 30% in the no boost group, compared to 76 ± 27% in the boost group ( p < 0.04). With a median follow-up of 17 months, 1 locoregional relapse was observed.

Conclusion: Helical tomotherapy reduces acute toxicity in the pre-operative radiotherapy of rectal cancer. A simultaneous integrated radiation boost increases the metabolic response, without excessive toxicity. This approach will be compared to chemoradiation in a randomized multicenter phase III trial.

P.83 MID-TERM ONCOLOGIC OUTCOMES OF CURATIVE RESECTION FOR LEFT-SIDED COLON CANCER OBSTRUCTION FOLLOWED BY STENT INSERTION

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Objectives: Self-expandable metallic stents (SEMS) have allowed an elective single-stage resection avoiding stoma formation in patients with left-sided colon cancer obstruction. But, there are not enough studies that demonstrate the oncologic outcomes of SEMS. The aim of study is to evaluate the short-term oncologic outcomes of curative resection for left-sided colon cancer obstruction followed by stent insertion.

Material and method: Between March 2005 and July 2008, 722 patients underwent surgical resection for colorectal cancer at Seoul St. Mary’s Hospital. Patients with right-sided colon cancer, rectal cancer, multiple primary colon cancer and inherited colon cancer were excluded. Then we include only stage II, III left-sided colon cancer patients who underwent curative resection. These selected patients were divided into three groups. 28 patients who underwent curative resection after SEMS insertion (group S) were compared to 77 patients who underwent elective surgery for nonobstructing left-sided colon cancer (group NO) and 37 patients with partial obstructing left-sided colon cancer (group PO). The clinicopathologic variables and survival rate were compared between three groups. The median follow-up period was 25 months.

Results: In our study, T stage was statistically different between the NO and PO+5 group (P=0.037). And neural invasion was statistically different between the PO and S group (P=0.048). Overall survival rate of between three group showed no statistically significant differences (NO vs PO+S; P=0.191, NO vs S; P=0.110, PO vs S; P=0.478). Disease free survival rates were also showed no differences between three groups (NO vs PO+S; P=0.352, NO vs S; P=0.094, PO vs S; P=0.182).

Conclusion: Stent insertion itself did not compromise the survival of patients with obstructive left-sided colon cancer. A further large-scaled prospective study and long term follow up is necessary to evaluate the oncologic safety of stent insertion.
P.84 RECONSTRUCTION OF THE PERINEUM AND/OR DORSAL VAGINA USING THE VERTICAL RECTUS ABDOMINIS MYOCUTANEOUS FLAP (VRAM) AFTER RESSECTION OF LOCALLY ADVANCED RECTAL CARCINOMA


Objectives: Treatment of primary or recurrent locally advanced rectal cancer consists of an aggressive multimodality approach. In our tertiary referral Center pre-operative chemo- and radiation therapy is combined with extensive surgery and Intra Operative Radiation Therapy (IORT). Resection of the dorsal vagina or the perineum may be necessary due to tumour invasion. Reconstructive procedures to close a defect after resection of the dorsal vagina or a perineal defect after an abdominoperineal have been described. The aim of this article is to describe our experience with reconstruction of the vagina or the perineum using the Vertical Rectus Abdominis Myocutaneous flap (VRAM) after resection of locally advanced rectal carcinomas (Fig. 1 and 2).

Method: All patients receiving vaginal and/or perineal reconstruction using VRAM flap were selected. Demographic data was collected, as well as data concerning type of resection. VRAM flap related complications, morbidity and mortality. All patients still alive were approached to fill out a questionnaire concerning satisfaction, quality of life and sexual function. Women alive were invited to the gynaecology department and underwent an interview and gynaecological exam by an also as sexologist trained gynecologist. Sexual dissatisfaction but also somatic problems; i.e. stenosis and dryness, were evaluated. Biopsies were taken from the neovaginal wall to evaluate the presence of nonkeratinizing mucosal type squamous epithelium.

Results: In the period 1994-2008 419 patients with a primary and 231 with a recurrent locally advanced rectal carcinoma were treated. 32 patients underwent reconstruction of the dorsal vagina and/or the perineum using a VRAM flap. 30 day mortality was 0%. In 1 patient necrosis of the skin island occurred, and in 4 patient a presacral abscess formed, what was drained without complications for the flap. 9 women took an gynaecological exam. 5 showed stenosis of the introitus. In 3 patients biopsy of the vaginal was taken, and pathological examination showed complete epithelialisation with nonkeratinizing mucosal type squamous epithelium.

Conclusion: The VRAM flap is a good reconstruction method for large defects in the dorsal vagina or perineum. Gynaecologic consultation at an early stage is advised.

P.85 CHEMOTHERAPY VS CHEMORADIOTHERAPY AS NEOADJUVANT TREATMENT FOR METASTATIC RECTAL CANCER: A STUDY OF LOCAL CONTROL

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Introduction: Treatment of stage-IV rectal cancer is controversial. In this setting, locally advanced tumors usually are found, so neoadjuvant chemoradiotherapy (CRT) may be necessary. In the other side, metastatic disease may have advantage of the use of more aggressive chemotherapy (CHT) or monoclonal antibody. The aim of the study is to compare the histologic regression and the local control of the primary tumor after both types of treatment.

Material and method: Between May-01 to July-09, resection of primary tumor after neoadjuvant treatment was performed in 27 patients in the setting of metastatic rectal cancer. We compare group A (N=11), formed by patients treated with oxaliplatin-based CHT (+ bevacizumab in 3 patients and cetuximab in two patients) and group B (N=16) formed by patients treated with CHT+5FU+ platinoprine-based CIFT). Circumferential margin involvement and local recurrence were studied to evaluate loco control. The evaluation of tumor response was performed based on Mandards classification.

Results: There were not differences with respect to age (62.3 vs 64.6 years; p=0.635) or tumor location (0-5/6-10/11-15 cm) (3/5/3 vs 2/8/6; p=0.391). Carcinemoygenenic antigen level was higher in group A (410 vs 57; p=0.002). Circumferential margin involvement was significantly low in group A (0% vs 56%; p=0.003). There were two local recurrences in group B and one in group A. Good response to neoadjuvany treatment (complete or near complete response) was observed in five patient of the group A and in one patient in the group B (45.4% vs. 6.2%; p=0.060). There were not differences in overall survival (26.7 vs 25.4 months; p=0.304).

Conclusion: Neoadjuvant treatment with oxaliplatin-based CHT +/- monoclonal antibodies had a lower rate of circumferential margin involvement and a better histologic response than CHT. There were no differences in local recurrence or overall survival.

Figure 1.

Figure 2.
THE INFLUENCE OF POSTOPERATIVE ILEUS FOLLOWING RECTAL SURGERY ON LENGTH OF HOSPITAL STAY AND PRESCRIPTION OF TOTAL PARENTERAL NUTRITION

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Objectives: Major rectal surgery is associated with a high incidence of postoperative ileus (POI). Early nutrition after colorectal surgery has a positive influence on postoperative recovery. If a patient develops ileus, oral and enteral feeding are impaired. A possible solution is Total Parenteral Nutrition (TPN). This study has been performed to describe the incidence of POI, the prescription rate of TPN and the incidence of possible complications due to TPN.

Method: Patients undergoing surgery for primary or recurrent rectal cancer, operated in 2008 were included in this analysis. Postoperative ileus was defined as the presence of nausea and/or vomiting, gastric retention (>500ml/24uur) and reinsertion of a gastric tube. Normal oral intake, administration of parenteral nutrition and first postoperative defecation were also registered. Furthermore we made an inventory of possible complications due to TPN, such as central line infection and bacteremia. A diagnosis of bacteremia was made if there was one positive blood culture associated with fever (temperature >38.3°C) or a white-blood-cell count greater than 12x10⁹/L that did not resolve after removal of a central-line catheter. A positive culture of a central line and resolution of fever after removal of the catheter is used to define a central-line infection.

Results: 50 patients were included in this retrospective study. 36% of these patients developed POI. Patients with ileus had a mean of 28 +/- 5 days in the hospital, by comparison with patients not experiencing ileus (11 +/- 5 days, p=0.007). Patients developing ileus received significantly more TPN as compared to patients without ileus (p=0.002). The total amount of days that patients received TPN was higher for patients experiencing ileus (17 +/- 5 days) in comparison to patients without ileus (6 +/- 1 days). Patients receiving TPN had a longer LOS compared to patients not receiving TPN (p=0.014). Moreover, 36% of all patients receiving TPN-developed complications such as a central line infection or bacteremia. The LOS of patients with bacteremia was 25 +/- 8 days, as compared to patients without bacteremia 13 +/- 2 days (p=0.015).

Conclusion: Postoperative ileus is an important problem after rectal surgery, causing a prolongation in LOS. Patients experiencing ileus receive more frequently TPN than patients without ileus. TPN was associated with a high incidence of bacteremia and central line infection related to the use of a central line. These complications might induce an increase in LOS.

P.68 COMBINED OXALIPLATIN AND CAPECITABINE RADIOCHEMOTHERAPY MORE EFFECTIVE THAN SOLELY 5FU BASED RADIOCHEMOTHERAPY

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Introduction: The addition of fluoropyrimidine chemotherapy to radiotherapy improves radical resection rate and hence reduces local recurrence but has not been shown to improve survival in rectal patients. The addition of a second chemotherapy agent has the potential to downstage the tumor more effectively, facilitate resection with clear margins, and may possibly influence micrometastases. Both oxaliplatin and capecitabine have proven activity in colorectal cancer and have radiosensitizing properties. The feasibility of using these two agents in combination with preoperative radiotherapy in patients with locally advanced rectal cancer has been demonstrated in fase 2 studies. Our institution is a referral center for advanced rectal cancer and was able to compare single fluoropyrimidine based radiochemotherapy (RCT) with the combination of oxaliplatin and capecitabine RCT.

Patients and method: Since 1999 RCT is the standard for advanced T3 tumors, which have on MRI no visible free margin between the tumor boarder and the mesorectal fascia, and T4 rectal cancers. Prior to the Mayo scheme (MS) consisting of bolus injections of 350mg 5FU/sqm during the first and fifth week of irradiation was used. Since our participation in a fase 2 study starting in 2003, the combination of 50mg/sqm oxaliplatin on each first day of an irradiation week with 850 mg sqm capecitabine twice daily became the standard in our institution. In the referring hospitals this scheme was not followed and many patients still received the MS, later replaced by monotherapy capectabine 825mg/sqm 2d. This did allow us to perform a comparison between the combination and single agent RCT. The pathology department used Quirke’s method of transversal slicing of the specimen.

Results: A total of 264 patients received RCT in the period from 1999-2009: 170 male and 94 female patients. The median age was 61 years. 97 patients had advanced T3 and 167 T4 tumors. Type of RCT was not different for T3 or T4 patients. After combined agent RCT 5.8% of the resections had involved circumferential margins, compared to 12% after single agent. The 5yr cancer specific survival, metastasis free survival and local recurrence rate for combined and single agent RCT were: 92% vs 64% (log rank p=0.046), 87% vs 62% (p=0.01), 6% vs 16% (p=0.013).

Conclusion: This study demonstrates that combination radiochemotherapy with oxaliplatin and capecitabine is more potent to downsize the tumor than solely fluoropyrimidine based RCT, as shown by the higher radical resection rate. Furthermore, which is a new finding, the oncological outcome parameters are all improved by the combination therapy. In advanced cases combination RCT should be considered.
P.08  THE RECTAL GIST: A RARE TUMOR ENTITY OF THE RECTUM

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Introduction: Gastrointestinal stroma tumours (GISTs) of the rectum are rare extramural tumours. They arise from the rectal wall and become identified during immunohistochemistry. However they should be considered as differential diagnosis when a neoplasm of the rectum is detected, since their symptoms may be similar to other malignancies in this region.

Material and method: We report three cases of rectal GISTs, diagnosed and treated at the Department of Surgery, University Hospital, Erlangen. The clinical, macroscopic, microscopic and immunohistochemical criterias, surgical and neo- or adjuvant therapy were investigated in a retrospective analysis.

Results: One case was found incidentally in a specimen resected for rectal adenocarcinoma. For the reason that it was benign only continuous monitoring was necessary. The other two cases were detected as primary diagnosis. One of these originated from the rectal wall and was presented as a tumour in the rectovaginal septum. It was diagnosed by a transvaginal biopsy. The patient underwent anterior resection and afterwards adjuvant Imatinib therapy. She developed recurrence in the pelvic cavity within a disease-free survival of 12 months. In spite of repeated Imatinib therapy, she had progressive disease, which was inoperable. Hereupon, adjuvant treatment was switched to Sunitib and is now under surveillance since 4 months with stable disease. The last case pertains to a rectal GIST, documented by a CT guided needle biopsy. The patient underwent abdomino-perineal excision but developed local recurrence after 72 months. By transperinal surgery the recurrent tumor was removed without residual tumor and the patient started Imatinib therapy. Since a surveillance period of 6 months there are currently no signs of recurrent tumour.

Conclusion: Rectal GISTs often present as extrarectal tumors or imaging suspicion of a retroperitoneal soft tissue sarcoma. Needle biopsy is essential to get the correct diagnosis. Clinically asymptomatic tumours probably represent advanced GISTs which need resection excision or are in doubt to be resected without residual tumour (R0). For that reason, neoadjuvant treatment with tyrosine receptor antagonists should be probably discussed more frequently.

P.09  PREDICTIVE VALUE OF RISK FACTORS FOR POST-OPERATIVE ANASTOMOTIC DEHISCENCES IN COLO-RECTAL CANCER RESECTIONS AND MULTIDISCIPLINARY THERAPEUTIC MANAGEMENT PRINCIPLES

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Background: This study intends to identify the risk factors involved in producing anastomotic dehiscences after resections for colo-rectal cancer, the value of a protective stoma and to highlight the therapeutic management principles, correlated to resurgery versus conservative medical treatment.

Patients and method: The study covers a period of 5 years, 2007-2011, with retrospective data for 2007 and prospectively in the period 2008-2011, of the 500 patients with mean age 55 years who have undergone a colorectal resection for rectal cancer; 10% have had emergency surgery for intestinal occlusion by stenosing rectal cancer and the remaining, elective surgery.

Results: The anastomotic dehiscence rate was 8% with a postoperative mortality from sepsis by 2.5%. Systemic risk factors identified were: age, malnutrition, secondary anaemia, lung associated disease, histopathologic type; all patients who had a protective stoma did not develop post-operative dehiscences. The initiation of conservative medical treatment in patients with anastomotic dehiscence has aimed to rebalance the medical treatment in patients with anastomotic dehiscence has aimed to rebalance the anemia, lung associated disease, histopathologic type; all patients who had a protective stoma did not developed post-operative dehiscences. The initiation of conservative medical treatment in patients with anastomotic dehiscence has aimed to rebalance the digestive circuit. In patients who had a protective stoma on the occasion of primary anastomosis, healing occurred at first. The anastomotic dehiscences remains a postoperative complication encumbered by a high mortality and huge costs of hospitalization, even in this century marked by the development of advanced/robotic surgery.

P.01  INITIAL EXPERIENCE IN ECORES (ENDOSCOPIC COLORECTAL SURGERY)

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Objectives: Local resection of colorectal lesions can be achieved through transanal endoscopic microsurgery (TEM), a safe technique.

A straight operating rectoscope is required, limiting the range to within 25cm from linea dentata. Some concerns have been expressed over the possible long term effects of the 4cm diameter rectoscope on fecal continence. Colposcopically resection is an alternative for local resections of gastrointestinal lesions, however piecemeal resection hampers histological evaluation. Endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) evolved, allowing intact resection. Both techniques use single instrument dissection and are associated with hemorrhage and perforation when applied in the thin walled colon. This may be overcome by reverting to bimanual dissection like in TEM so we can present the tissue with one instrument during controlled dissection with the other. The objective of our research was to develop a safe alternative to TEM on a flexible endoscopic platform. Secondary objectives were the description of a standard ECORES procedure and selection of an ECORES instrument kit.

Method: A double work channel flexible endoscope (the R-Scope) was applied in our tests. This 13mm diameter flexible endoscope allows for application of two independently maneuvered instruments up to over 180cm from linea dentata. The Hybrid Knife is an instrument that can apply hydro-dissection as well as diathermia. The mucosa can be raised by injecting water, decreasing the chances of perforation. Then selecteive diathermia of the submucosal vessels that remain after hydro-dissection can be performed without having to change instruments. Various Hybrid Knife models were assessed. Initially ECORES was performed on an in vitro model mounted with bowel resects in order to develop a standard technique. The live porcine model was subsequently operated on in order to research the effectivity of hemostasis and the results of peristalsis.

Results: A standardized procedure was developed on the in vitro model in which the Hybrid knife allowed for the fastest and safest dissection. The T-tipped model offered most safety as it can be hooked onto tissue before controlled dissection. Rat tooth 19.5mm forceps were the preferred instrument for tissue presentation during dissection due to their grip and the stiffness of the tip that allows for traction at a distance from the scope. During practice sessions single-piece mucosa resections rapidly increased to 6cm diameter. When performed in vivo hemostasis was adequate and large single-piece resection was possible though maintaining oversight proved challenging due to peristalsis.

Conclusion: ECORES is technically possible and a standard procedure has been formulated. It allows for controlled dissection and may well offer a safe alternative to ESD and EMR. Further in vivo studies are required to asses the safety of this technique.

Figure 1. ECORES.
P.92 MULTICENTRE PHASE II CLINICAL TRIAL OF YTTRIUM-90 RESIN MICROSPHERES ALONE IN UNRESECTABLE, CHEMOTHERAPY REFRACTORY COLORECTAL LIVER METASTASES

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Objective: To evaluate prospectively the efficacy and safety of radioembolisation (also known as selective internal radiation therapy, SIRT) in patients with unresectable, liver-dominant colorectal liver metastases (mCRC) who failed prior oxaliplatin- and irinotecan-based systemic chemotherapy regimens.

Method: Eligible patients had adequate hepatic, hemopoietic and renal function, and an absence of major hepatic vascular anomalies and hepato-pulmonary shunting. Gastroduodenal and right gastric arteries were embolised prior to hepatic arterial administration of a single treatment of yttrium-90 resin microspheres (SIR-Spheres; Sirtex Medical Limited, Sydney, Australia) (median activity, 1.7 GBq; range, 0.9-2.2 GBq).

Results: Of 50 eligible patients, 38 (76%) had received 24 lines of chemotherapy. Most presented with synchronous (stage IV) disease (72%); >4 hepatic metastases (58%); (median size, 50 mm); 25-50% replacement of total liver volume (60%) and bilateral spread (70%). Baseline analysis of biopsies of neoplastic cells obtained from 26 patients found 96% were positive for p53, 83% for Survivin and 42% for bcl-2. A high Ki67 index was recorded in 74% of 19 patients evaluated. By intention-to-treat analysis using RUCIST, 1 patient (2%) had a complete response, 11 (22%) a partial response, 12 (24%) stable disease, 22 (44%) progressive disease, and 4 (8%) were non-evaluable. Median overall survival after radioembolisation was 13 months (95% CI, 7-18), with a 2-year survival of 19.6%. Pre- and post-treatment analysis of biopsies from 13 patients found favourable changes in all biomarkers following radioembolisation, although these changes were only significant (p=0.05) for p53 and bcl-2. Early and late (>48 hour) WHO CT-2 adverse events (mostly febrile and pain) were observed in 16% and 22% of patients, respectively. Two patients died due to renal failure at 40 or liver failure at 60 days, respectively.

Conclusion: Radioembolisation produced meaningful response rates and disease stabilisation in patients with advanced, unresectable mCRC who had exhausted all standard therapeutic options. Provisional evidence indicates evidence of choral selection post-radioembolisation; although the significance of these changes on the clinical outcome requires further analysis in larger patient groups. Further investigation of yttrium-90 resin microspheres in combination with modern systemic chemotherapy earlier in the course of the disease is warranted.

P.93 OPTIMAL TIME FOR SURGERY FOLLOWING PREOPERATIVE SELF-EXPANDABLE METALLIC STENT INSERTION IN PATIENTS WITH OBSTRUCTIVE COLORECTAL CANCER

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Objective: Self expandable metallic stent (SEMS) has been increasingly used as an option for decompression of obstructive colorectal malignancy. This study was aimed to determine the optimal time of surgery after preoperative stent insertion for obstructing primary colorectal cancer (CRC).

Method: From January 2000 to September 2008, 62 patients (35 males and 21 female, mean age of 62 years) with obstructive primary CRC were treated with preoperative placement of SEMS followed by elective surgery. Patients were categorized into two groups according to the time interval between SEMS insertion and operation: Group A, patients operated within 7 days of SEMS placement (N = 26); Group B, patients operated after 7 days of SEMS placement (N = 30). We analyzed operative morbidity, mortality, and factors related to postoperative recovery including operative time, time of the first bowel movement, time of starting normal diet, and length of hospital stay.

Result: No technical failure and 6 clinical failures (9.6%) were observed. Causes of clinical failures were insufficient expansion of SEMS in 3 patients, bowel perforation for 2 and pelvic abscess in one. Location of tumor was sigmoid colon in 36 patients, descending colon in 13, rectum, in 6 and transverse colon in one. Operative morbidity occurred in two patients of Group A (7.7%, 1 rectovaginal fistula and 1 chylous ascites) and in 5 of Group B (16.7%, 2 postoperative ileus, 2 pneumonia and 1 pleural effusion; P = 0.532), and one mortality occurred in Group B. There was no significant difference in terms of factors associated with postoperative recovery between the two groups.

Conclusion: Although the study population was not large, our data suggest that once the patients with obstructive primary CRC are successfully decompressed by preoperative SEMS, early surgical intervention within 7 days after placement of SEMS is feasible with acceptable postoperative morbidity and no delayed recovery.

P.94 EVALUATING THE ROLE OF A MULTIDISCIPLINARY TEAM DISCUSSION IN THE OUTCOME OF RECTAL CANCER TREATMENT

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Objectives: The patient-tailored approach in rectal cancer treatment is emerging. To analyse the additional value of discussing rectal cancer patients in a multidisciplinary team (MDT) we evaluated the type of neoadjuvant treatment given in correlation with the occurrence of positive circumferential resection margins (CRM).

Method: All treated rectal cancer patients (>Ti, Nx, 2 or M0) diagnosed between 2006 and 2008 were included. According to the national guidelines, neoadjuvant (chemo)radiotherapy should be given to all those patients. Patients with a threatened CRM (T4c or T4) should receive chemoradiotherapy (CRT); all others should receive short course radiotherapy (SCRT; 5 Gy). Patients from 1 radiotherapy referral centre and 6 referring hospitals were evaluated and were scored as “discussed” (MDT+) only if documented proof was available. The primary endpoint was the number of positive CRM’s, defined as tumour ≤1 mm from the CRM. Due to incomplete documentation of the CRM, the R0/R1 classification (tumour in the resection margin) was also analysed.

Results: Of the 275 patients included, 224 were analysed (exclusions: (recto)sigmoid tumour (n=26), acute laparotomy (n=1), inoperable (n=24)). Total mesorectal excision (TME) was performed in 221 patients. Neoadjuvant (CRT) was applied in 184 (82%) patients. In the MDT+ (119/224 patients) group, magnetic resonance imaging (MRI) was performed in 92% versus 73% in the MDT- group (p=0.001). Clinical TNRN staging was more complete in the MDT+ group (94% versus 75%, p=0.001). The proportion of patients with more advanced disease (T3 and/or N+) was higher in the MDT+ group, 85% versus 69% (p=0.002). Correlation of the clinical and pathological T and N stages of the patients not receiving CRT (i.e. no downstaging expected) revealed a staging accuracy for T-stage of 56% and N-stage of 61%. Table 1 shows CRM involvement and R0/R1 classification according to neoadjuvant therapy and MDT discussion. In 9/221 operated patients and in one patient irresectable after CRT (* in the table) an R1-resection was documented. CRM was reported in 126/221 (67%) patients. CRM-positivity did not differ between both groups.

Conclusion: Surgeons seem to select mainly advanced disease patients for MDT discussion. However, the high staging inaccuracy and the relatively high incidence of CRM involvement in patients receiving short course radiotherapy calls for both further training of the MDT and an increase in the number of patients discussed.
P.95 DURABLE DISEASE-FREE SURVIVAL WITHOUT RESECTION OF TARGET LESIONS FOLLOWING RADIOEMBOLISATION WITH YTTRIUM-90 RESIN MICROSPHERES IN PATIENTS WITH COLORECTAL LIVER METASTASES

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Objectives: Despite marked improvements in systemic therapy for advanced colorectal cancer (CRC), patients with liver metastases will ultimately die of their disease unless they are successfully resected. Complete responses resulting from chemotherapy treatment will typically add less than 12 months to the overall survival figure for this group of patients. Radioembolisation with yttrium-90 resin microspheres (also known as selective internal radiation therapy or SIRT) delivers therapeutic doses of radiation to liver tumours while sparing the normal liver parenchyma. The effect of radioembolisation as a treatment supplement has demonstrated improved response rates in 5 published prospective trials in patients with CRC liver metastases. As chemotherapy combined with radiotherapy can be curative for some solid tumours, we explored whether this could be achieved using radioembolisation in patients with CRC liver metastases with liver as the dominant or only disease site.

Method: A retrospective review of ~200 cases was conducted at five centres with radioembolisation experience to identify complete responders who survived beyond 3 years.

Results: The review identified 7 patients with unresectable and unresected metastatic CRC liver metastases who remain alive and disease-free 5 to 10 years following radioembolisation. Six patients received radioembolisation first-line for their liver metastases (2 patients as monotherapy; 4 with FU). One patient received radioembolisation plus irinotecan as a third-line treatment. Five patients had bilobar radioembolisation, one patient could only be treated in one of the diseased lobes of the liver due to an aberrant hepatic arterial anatomy that could not be corrected. The seventh patient had disease confined to one lobe of the liver. Median time from treatment to the disappearance of all lesions (based on serial computed tomography imaging) was 6 months (range 3-48 months). The median duration of complete responses is 75 months (range 54-99 months) from the time of recorded response. At the time of reporting, no patient had progressed and all were alive after a median follow up of 85 months (range 60-123 months).

Conclusion: Prolonged disease control, and possibly cure, can be achieved following radioembolisation (with or without chemotherapy) in patients with CRC liver metastases, particularly when used as a first-line treatment. The frequency of this occurrence would appear, on this review, to favour patients with fewer prior lines of chemotherapy. Long-term follow-up from data of prospective trials that include patients with liver-only disease are required to define the frequency of this event.

P.96 RETROSPECTIVE STUDY TO EVALUATE EFFICACY AND SAFETY OF BEVACIZUMAB IN COMBINATION WITH BIWEEKLY XELIRI AS FIRST-LINE TREATMENT IN METASTATIC COLORECTAL CANCER

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Background and objectives: Bevacizumab (BEV) is the cornerstone of first line treatment for colorectal cancer (CRC). BEV combined with irinotecan and S- fluorouracil (S-FU) improves response and survival with an adequate safety profile. In our practice, biweekly XELIRI schedule (irinotecan and capcitabine) achieves high efficacy with low toxicity. Our purpose was to evaluate the efficacy and safety of BEV combined with biweekly XELIRI regimen as first-line treatment for CRC, therefore replacing S-FU by capcitabine, a prodrug as effective as the former in continuous infusion.

Method: Observational, retrospective, uncentered study in patients with metastatic CRC treated with BEV and biweekly XELIRI. Results: A total of 46 evaluable patients were enrolled in this study. Patients characteristics: median age: 64 years (39-80); male/female: 21 (46%) vs 25 (54%); Performance Status: 1: 35 (82.6%); primary tumor location: colon: 15 (36%), rectum (30.4%), rectosigmoid (26.1%), synchronous (8.7%); metastatic sites: 1 (47.8%), 2 (39.1%), 3 (13%), liver metastasis location: liver (65.2%), lung (39.1%), lymph nodes (37%), peritoneum (13%), others (52.6%). 28.3% of patients received previous adjuvant treatment, with a median of 5 cycles. 8 patients (17.4%) underwent surgical resection of liver metastases and 5 (11%) underwent surgery of extra hepatic metastases. A total of 586 cycles were administered with a median of 11.8 cycles per patient for BEV and capcitabine and 12.5 for irinotecan. 54.3% of patients needed at least one delay of BEV and 41.3% and 37% of patients required at least one dose reduction of capcitabine and irinotecan respectively. Response rates: 31 patients (67.4%) achieved global response: 2 (4.3%) had complete response and 29 (62%) partial response; 12 (26%) reached disease stabilization and 3 (6.5%) progressed. Progression-free survival was 12.3 months. Median overall survival was 23.7 months. Most frequent grade 3-4 toxicities were alopecia (13%), nausea (8.7%), asthma, diarrhea and vomiting (6.5%).

Conclusions: The combination of BEV plus biweekly XELIRI is an active first-line treatment for CRC that achieves potential results in terms of response and survival and shows an adequate safety profile, with a low rate of toxicity.
Conclusion: Wide excision of the rectum including the pelvic floor and adjacent structures that are in proximity to the rectal carcinoma after tailored neoadjuvant treatment and guided by adequate imaging studies yields a free CRM and definitive local tumour control in a very high proportion of patients. The perianal wound of elliptical excision can be managed by simple suturing.

Results: Data cut-off for this interim analysis was 15 Oct 08; cut-off for the primary analysis to be presented will be 18 Jun 09. Recruitment completed Jun 08 with 154 pts enrolled. KRAS evaluable samples are available for 92% of pts and EGFR samples for 84% of pts. Of the 85 pts with KRAS wt tumours, and the 57 pts with KRAS mutant (mt) tumours 78%/54% are male; median age is 64 years (range 21-84)/66 years (range 37-80) and 95%/93% of pts had ECOG PS 0-1, respectively. As of 15 Oct 08, 37 (44%) pts with wt tumours, 24 (42%) pts with mt tumours and 4 (33%) pts with tumours with unevaluable KRAS status were still receiving at least one element of combination therapy. The most common reason for discontinuing panitumumab treatment was disease progression (17 pts [20%] wt subset; 14 pts [25%] mt subset). Median follow-up was 25.9 months and 24.7 months and response rate was 48% and 29% in the KRAS wt and mt subsets, respectively. KRAS status does not appear to influence incidence of adverse events. There were three reported grade 5 events (haematemesis, rectal haemorrhage, vena cava thrombosis).

Conclusion: Combining panitumumab with FOLFIRI in the first-line setting appears to be a well-tolerated regimen. The primary analysis (cut off 18 Jun 09) will be presented at the congress with updated data for the primary and secondary endpoints.

Table 1

<table>
<thead>
<tr>
<th>Panitumumab + FOLFIRI</th>
<th>Adverse Event (any grade)</th>
<th>KRAS wt (n = 85)</th>
<th>KRAS mt (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous (all)</td>
<td>10 (12)</td>
<td>53 (93)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (10)</td>
<td>10 (18)</td>
<td></td>
</tr>
<tr>
<td>Infecction (all)</td>
<td>9 (11)</td>
<td>38 (67)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (18)</td>
<td>29 (51)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (2)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>3 (5)</td>
<td></td>
</tr>
</tbody>
</table>

P.99 PRIMARY ANALYSIS OF A PHASE II, SINGLE-ARM STUDY (2006031) COMBISING PANITUMUMAB WITH THE FIRST LINE TREATMENT OF PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (MCRC)

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Background: Panitumumab is a fully human anti-epidermal growth factor receptor monoclonal antibody with proven monotherapy activity in pts with wild-type (wt) KRAS-expressing mCRC. This first-line, single-arm phase II study in pts with wt mCRC was designed prospectively evaluating if KRAS status predicts response with panitumumab and FOLFIRI.

Method: Pts with histologically confirmed mCRC (no prior systemic treatment) and ECOG PS 0-2 were enrolled at 41 European sites to receive panitumumab (8mg/kg) plus FOLFIRI every 2 weeks. The primary endpoint is objective response rate; secondary endpoints include disease control rate, duration of response, time to response, progression-free survival, time to progression and safety.

Objectives: Panitumumab is a fully human anti-epidermal growth factor receptor monoclonal antibody with proven monotherapy activity in pts with wild-type (wt) KRAS-expressing mCRC. This first-line, single-arm phase II study in pts with wt mCRC was designed prospectively evaluating if KRAS status predicts response with panitumumab and FOLFIRI.

Method: Pts with histologically confirmed mCRC (no prior systemic treatment) and ECOG PS 0-2 were enrolled at 41 European sites to receive panitumumab (8mg/kg) plus FOLFIRI every 2 weeks. The primary endpoint is objective response rate; secondary endpoints include disease control rate, duration of response, time to response, progression-free survival, time to progression and safety.

Results: Of 88 patients, 11 patients (13%) underwent elective surgical resection of the primary tumor without adjuvant chemotherapy; 15 patients (17%) received both elective resection and chemotherapy, 21 patients (24%) underwent palliative chemotherapy and 41 patients (47%) received supportive care, consisting of radiotherapy, stenting or placement of AF. Of the 88 patients, 86 have died during the study period with an overall median survival time of 357 days. Patients treated by resection without adjuvant chemotherapy did not significantly have better survival than patients treated with chemotherapy alone (p=0.4); survival in these groups was better than in patients receiving supportive care (p=0.01). Patients treated by resection and chemotherapy had better survival than patients receiving chemotherapy (p=0.01) or surgery alone (p=0.003) (figure). Comorbidity and liver involvement were not different per treatment modality (p=0.54 and p=0.2, respectively). Metastatic liver involvement was not correlated with worse survival (p=0.07) and comorbidity was borderline significantly correlated (p=0.058). For patients undergoing resection, mean hospital stay was 27 days. Perioperative morbidity was seen in 9 patients (38%). No patients died within 30 days after surgery. Of patients receiving chemotherapy, six (17%) discontinued chemotherapy because of severe side effects, of which 1 (3%) died from DPD deficiency.
P.101 SURVIVAL OF COLORECTAL CANCER IN IRAN
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Objective: Colorectal Cancer is the forth cause of cancer after stomach, bladder, prostate in men and second cause after breast in women in Iran. It is estimated to occur 4000 new cases each year with 1150 death annually. Here we are going to introduce the survival of colorectal cancers in Iran in a national manner.

Method and results: The data from national cancer registry department of Ministry of Health and Medical Education (MOH&ME) were used as the main source of incident colorectal cancer in Iran from March 2000 to March 2005. One and five year survival was 88% and 45% for females versus 86% and 39% for men. The median overall survival for colorectal cancer in Iran was 3.5 years with Confidence Interval 95% (3.2-3.8 years).

Conclusion: The overall 5 year survival for colorectal cancer in Iran (41%) is comparable even with some developed country but it is far from the countries with advanced health care system, or community based screening program. Thus on policy level application of an appropriate national cancer control program and management guidelines should be under consideration.

Figure 1. Overall Survival for 2192 cases of Colorectal.
Figure 2. Overall Survival for 2192 cases of Colorectal.

P.102 LOW ANTERIOR RESECTION FOR RECTAL CARCINOMA: OUR EXPERIENCE
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Objective: Aim of this study was showed our institution’s experience with low anterior resection in combination with coloanal anastomosis for primary rectal cancer. We were reviewed: to determine cancer treatment results, to identify risk factors for pelvic recurrence, and to assess the long-term success of sphincter preservation.

Method: In the period 2000 - 2009, 200 patients with rectal cancer were operated in the General hospital ‘Sveti Vracevi’ in Bijeljina. Sphincter saving procedures (SSP) were performed in 70%, abdominoperineal resections (APR) in 24%, and resection of rectum with definitive stoma (Hartman procedure) in 6% patients.

Results: In the group of patients where SSP was performed (140 cases) there were 29% high colorectal anastomoses (8 cm from anal verge), 64% with low (4-8 cm from anal verge) and 7% with intraabdominal colorectal anastomosis. 31 patients were relapsed.

Local recurrence was detected in 8 patients. SSP group was also divided into two subgroups; first group total mesenteric excision (TME) and second group transection of mesocolon was carried out. Local recurrence in TME group was 7%, in the transaction group 5%. In APR group recurrence was registered in 31%. Mesenteric implants, positive microscopic resection margin, T3 tumor, perirectal and blood vessel invasion, high tumor grade were associated with increased risk for pelvic recurrence. Six patients ultimately required permanent colostomy. Postoperative mortality was 1.6 %, and clinical leak rate was 7.3 %. Local recurrence rate was significantly higher in patients more than 65 years old (14 vs.1%; P <0.005) and in patients with resection margins less than 2.0 cm (17 vs.5.5 %; P <0.05). Ten-year survival was 52 %.

Conclusion: Low anterior resection combined with coloanal anastomosis provides good treatment for rectal cancers. We believe that performing SSP should be encouraged whenever it is possible. Resection margins of more than 2 cm are necessary. Long-term preservation of anal sphincter function depends primarily on control of pelvic tumor and can be achieved in more than 90% of patients.

P.103 PROGNOSTIC SIGNIFICANCE OF IMMUNOHISTOCHEMICAL MARKER PROFILE IN COLORECTAL CANCER
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1General hospital Sveti Vracevi Bijeljina, Bijeljina, Bosnia-Herzegovina; 2Clinical Center Banja Luka, Clinic of Oncology, Banja Luka, Bosnia-Herzegovina

Objective: Our aim was to examine whether certain immunohistochemical molecular markers, specifically PCNA, Ki-67 and p53, could be used to predict the tumoral response of rectal cancer to determine the overall and disease-free survival rates of patients following adjuvant therapy.

Patients and method: In ‘Sveti Vracevi’ Hospital in Bijeljina 301 patients suffering from colon cancer received treatment from 1st January 2000 to 31st December 2008. We analyzed the prognostic value of PCNA, Ki-67, and p53 by immunohistochemistry on formalin-fixed, wax-embedded sections in a series (n = 153) of stage III (Dukes C) colorectal cancers. An immunohistochemical score based on the intensity of immunoreactivity and, where relevant, the proportion of immunoreactive cells was established for each marker. We elected to investigate PCNA, Ki-67 as a marker of cell proliferation indices and p53 oncoprotein/tumor suppressor gene because these markers have been demonstrated in a number of studies to have potential value in defining populations of individuals who either may or may not benefit from the use of adjuvant chemotherapy.

Results: Using 9 years of follow-up data, our retrospective analysis demonstrated an association between PCNA intensity (relapse-free survival [RFS]; risk ratio [RR] = 1.47, P<0.01; overall survival [OS]; RR= 1.49, P =0.002), Ki-67 (RFS: RR = 0.71, P = 0.05; OS: RR = 0.6, P =0.05), and p53 (RFS: RR = 1.42, P=0.01; OS: RR = 1.19, P =0.005) for RFS and OS. High PCNA intensity levels and positive p53 staining were associated with a worse outcome. Tumors containing a high percentage of Ki-67-positive cells enjoyed an improved outcome compared with those patients whose tumors contained relatively few positive cells. An interaction with treatment was not identified for any of the markers.

Conclusion: Immunohistochemical analysis is not used in the routine analysis of colon cancer. This retrospective investigation demonstrated that PCNA, and p53 staining each had significant prognostic value for patients colon carcinoma. There was not statistically significant difference in the survival rate of patients with positive immunohistochemical Ki-67 values in relation to the patients with the negative values.
The aim of the study was to evaluate the analogic effect of zolendronate (a third generation bisphosphonate) in patients with colorectal cancer (cc) and bone disease.

Patients and Method: 28 cc patients with metastatic bone lesions were evaluated for pain evolution during treatment with zolendronate. Pain is assessed with a 10-point visual analogue scale (VAS) at every cycle. Zolendronic acid 4mg was administered as an intravenous 15-minute infusion (diluted with 250ml of 0.9% sodium chloride solution) repeated every 4 weeks.

Results: The majority of patients (71%) obtained a decrease of pain intensity after the administration of the first 2 infusions (2 months of treatment) of zolendronate. VAS score ranged from 3.5 to 5 at baseline. Median change in pain scores was 1.2. The use of analgetic drugs also decreased in 9/28 patients. The most common adverse events about 24-48 hours after the infusion were fever (23% patients), arthralgias and myalgias (9% patients), nausea (3% patients) and hypocalcemia (4% patients, about 7 days after the infusion). However, zolendronate was generally well tolerated in cc patients.

Conclusion: Zolendronic acid seems to have an analogic effect and to improve quality of life for cc patients with metastatic bone disease.

P.105 PSYCHOSOCIAL ASPECTS IN COLORECTAL CANCER PATIENTS STAGE Dukes B2 C

The aim of this study was the evaluation of quality of life (QOL) in colorectal cancer (cc) patients stage Dukes B2 & C, who received adjuvant chemotherapy after surgery.

Patients and method: In our study 56 cc patients, 30 male and 25 female, median age 46 years old, 4 years disease free, were entered. All patients answered in a short questionnaire about QOL during and after treatment. Only 50 cc patients answered the questions in complete form.

Results: The diagnosis signified a psychological distress in all cc patients. All patients presented anxiety, anguish or reactive depression in different grades. Sexual activity was very poor or null during adjuvant treatment. Sexual activity was normal in 70% of cases, 6 months after end of adjuvant chemotherapy. Because of alopeia 81% and weight gain all had negative felling about self corporeal image. Younger cc patients recovered earlier (healthy state) and social activities after adjuvant chemotherapy. Adjuvant chemotherapy was recognized as the most aggressive treatment. In spite of these data, most of cc patients refused psychological assistance.

Conclusion: Even in cc patients with possible cure and good manage of treatment and toxicities, quality of life was clearly affected in this group of cc patients.

P.106 SEXUAL DISORDERS IN PATIENTS TREATED FOR COLORECTAL CANCER

The aim of the study was the development an anonymous questionnaire to study the sexual disorders and related problems of patients operated for colorectal cancer (cc), followed by adjuvant therapy.

Patients and method: We studied 40 (22 men - 18 women) cc patients. The average age was 48.25 (standard deviation 7.23, range 32-64). The cultural level was average: 30% elementary school education, 34% high school education, 2% graduates. All were married. 88% had one or more children. At the time of the study all the cc patients were disease free and had finished chemotherapy at least one year before.

Results: In 36% of cases the sexual disturbances were present before the surgery. In 11% sexual disturbances worsened, in 35% they were constant. After the operation, 65% of the patients graded their sex life qualitatively good, 30% fair and 5% poor. After the operation these gradings were: 21% good, 40% fair and 12% poor. 13% were no longer sexually active following the operation.

Conclusion: In the overall view of side effects of cc treatment, sexual disturbances have a significant role, even though the patients describe an improvement in their affectionate relationship with their partner. Doctors must give greater attention to and discuss with the cc patient their sexual problems with the realm of side effects in the planning of the treatment for colorectal cancer.

P.107 THE ROLE OF LIPID PROFILE IN THE PROGNOSIS OF THE COLORECTAL CANCER (CC) PATIENTS

The aim of the present study was to analyse the lipid profile of individuals with cc and to follow serum lipid levels changes in cc patients according to their response to chemotherapy.

Patients and method: 33 patients, one control group, composed of 32 age- and sex-matched healthy adults, related to cc patients, respectively, were included in the study.

Follow-up studies of cc patients were carried out after the 3rd and 6th cycle of chemotherapy.

Results: Initial plasma Cholesterol (Chol), HDL-Cholesterol (HDL-Chol) and Phospholipids (PL) values were significantly lower in cc patients than in controls (p<0.001). Following chemotherapy, we noticed a progressive increase in lipid levels in cc patients with complete remission (CD) and stable disease (SD), and further decrease in patients with the disease progression.

Conclusion: Decreased plasma Chol, HDL-Chol and PL levels of patients with cc can be considered as non specific prognostic parameters in patients with colorectal cancer.

Table 1

<table>
<thead>
<tr>
<th>Chemotherapy Cycles</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Pts Rx'd</td>
<td>105</td>
<td>63</td>
<td>45</td>
<td>27</td>
<td>21</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>No Vomiting</td>
<td>58</td>
<td>44</td>
<td>29</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td>4</td>
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<td>No Diarrhea</td>
<td>58</td>
<td>79%</td>
<td>64%</td>
<td>59%</td>
<td>52%</td>
<td>56%</td>
<td>50%</td>
</tr>
<tr>
<td>No Nausea</td>
<td>37</td>
<td>32</td>
<td>24</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>39%</td>
<td>52%</td>
<td>57%</td>
<td>50%</td>
<td>45%</td>
<td>43%</td>
<td>12%</td>
</tr>
</tbody>
</table>

P.108 USE OF PALONOSETRON I. V. IN CONTROLLING NAUSEA AND VOMITING ASSOCIATED WITH MULTIPLE CYCLES OF EMETOGENIC CHEMOTHERAPY IN COLORECTAL CANCER (CC) PATIENTS

The aim of this study was to evaluate the palonosetron (P) (250 micrograms intravenously) in control of nausea and vomiting in cc patients, after emetogenic chemotherapy.

Patients and method: 105 cc patients who had achieved emetic control with P during one cycle of high dose oxaliplatin-based chemotherapy and who were scheduled for repeat cycles were entered into this single-dose open label study. They received 250 micrograms of P intravenously over 5 minutes, ending 30 minutes before the infusion of oxaliplatin. The patients were observed for the severity and time of onset of nausea or vomiting on an inpatient basis for the first 12-24 hours. Assessment of nausea and vomiting continued on an outpatient basis for 3-8 days following discharge.

The proportion of patients remaining nausea-free and vomiting-free at discharge was comparable over each cycle.

Results: Adverse events considered related to P included headache (6 reports) and constipations (2 reports).

Conclusion: Overall palonosetron was well tolerated and effective in the treatment of chemotherapy-induced nausea and vomiting and repeated use of palonosetron did not reduce its effectiveness.

P.109 THE OUTCOME AND PROPRIETY OF SURGICAL TREATMENT OF COLORECTAL CANCER IN THE ELDERLY

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Ewha Womans University, Seoul, South Korea

Purpose: As the Life expectancy increases, elderly colorectal cancer patients are also increasing. Compared to younger patients, elderly manifest higher co-morbidity with more advanced and emergent disease. However, recent studies have studied have reported similar surgical approach irrespective of age distribution. We evaluated the outcome and propriety of surgical treatment of colorectal cancer in the elderly patients.

Method: The medial records of 464 colorectal patients, who underwent surgery during 2003 to 2007 in Ewha Womans University Mokdong hospital were reviewed retrospectively. The patients were divided into three group according to the age distribution : I-younger than 70, 70, II 71-80, III older than 81. Clinical and pathological characteristics, surgical outcome and survival rate were analyzed.

Result: 338 patients were belonged to group I, and 104 patients to group II, and group III included 22 patients. Although, male patients were more prevalent in all three groups.
group, female distribution was slightly higher in group III (P=0.055). Clinical characteristics among the three groups did not reveal specific differences except TNM stage distribution. In group I and II, patients with stage II (AI), stage III (AII) and stage IV (AIII) were most common compared to group III, in which most frequent in III. Also, the histologic classification of the postoperative morbidity rate did not show differences among the three groups. The survival rate was lowest in Group III but no significant. However, emergency operation was more frequent in group III (P=0.02), in accordance with increased postoperative complication (P=0.005).

Conclusion: Our results demonstrated comparable operative morbidity and mortality, and emergency operation was the only significantly influencing factor in the surgical outcome. Therefore, we can conclude that in colorectal cancer patients, surgical treatment is no longer contraindicated.

P.110 PHARMACOGENETIC TAILORED FIRST-LINE CHEMOTHERAPY IN ELDERLY PATIENTS WITH ADVANCED COLORECTAL CANCER. A PHASE II, PROSPECTIVE STUDY

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Introduction: Retrospective analyses suggested that a pharmacogenetic approach may allow a tailored selection of chemotherapy for metastatic colorectal cancer. We conducted a phase II study of pharmacogenetic-selected first-line chemotherapy in elderly patients with advanced colorectal cancer. Aim of the study was to improve efficiency and to reduce toxicity.

Patients and method: Chemotherapy regimen was prospectively assigned based on TS, DPD, ERCC-1 and UGT1A1 genotyping results.

Results: Twelve patients (50%) were treated with modified FOLFOX, 11 patients (46%) with POLFOx and 1 (4%) with the modified De Gramont regimen. A partial remission was obtained in 4 cases (17%), stable disease in 8 cases (33%) and progressive disease in 12 cases (50%). Grade 3-4 neutropenia was observed in 7 patients (29%) and diarrhea in 3 cases (12%). The trial was then interrupted according to the study design 19 partial remissions out of the first 24 patients enrolled as the necessary response rate level in order to continue.

Discussion: Prospective selection of chemotherapy based on TS, DPD, ERCC-1 and UGT1A1 expression in elderly advanced colorectal cancer patients failed to confirm previous results. A more accurate validation of retrospective findings should be performed before prospectively selecting the appropriate treatment for the appropriate patient.

P.111 ‘WAIT-AND-SEE’ POLICY IN CLINICAL COMPLETE RESPONDERS TO CHEMORADIATION IN RECTAL CANCER: A PROMISING ALTERNATIVE

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Objectives: Neoadjuvant chemoradiation for locally advanced rectal cancer increasingly results in a complete response (pCR). Complete responders surgery may safely be omitted and patients could undergo intensive follow up in cases of a wait-and-see policy. In order to safely select patients for wait-and-see, it is essential that the response evaluation after chemoradiation is accurate enough to select the appropriate candidates. The purpose of this study was to determine whether patients with a clinical and radiological complete response that undergo wait-and-see (and intensive follow-up with MRI) have a comparable prognosis as compared to patients with a pathological complete response (pCR) after surgery.

Method: After chemoradiation patients underwent standard T2-weighted MRI at 1.5T to evaluate the response to therapy. In case of a complete response at MRI, patients underwent endoscopy + biopsy to confirm the MRI outcome. When both MRI and endoscopy indicated a complete response, patients were offered a wait-and-see policy, with intensive follow-up, consisting of 6-24 weekly MRI, endoscopy and laboratory examinations. The pCR-control group was identified from a multicenter prospective rectal cancer cohort-study.

Results: 12 clinical complete responders (median age 63) were identified and offered a wait-and-see policy. Median follow-up for this group is 20 months (range 2-56). Two patients from the wait-and-see group had synchronous liver metastasis at diagnosis, treated with curative intent. 15 patients (median age 67) with pCR after surgery were identified from the control-group, with a median follow-up of 32 months (range 8-53). One patient from the wait-and-see group developed recurrent liver metastasis and a possible local recurrence. In the pCR-control group one patient developed lung metastasis and one patient died of pneumonia. All other patients for both groups are disease free and alive. Overall survival is 100% for the wait-and-see patients and 92.9% for the pCR-patients.

Conclusions: A wait-and-see policy for clinical complete responders to neoadjuvant chemoradiation is a promising and potentially feasible alternative to standard surgical treatment. Identification and follow-up of these patients with MRI is feasible.
P.114 COMBINATION OF TWO MINIMALLY INVASIVE PROCEDURES FOR OBSTRUCTION OF THE LEFT COLON: ANOTHER ALTERNATIVE TO THE HARTMANN PROCEDE
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1Santa Cruz de Tenerife, Spain; 2Department of Surgery, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

Objectives: Resection of the colonic segment involved and the construction of an end colostomy (Hartmann’s procedure) is the most frequent treatment in the obstruction of the left colon. Other alternatives to the Hartmann procedure are subtotal colectomy or intraoperative lavage of the colon and primary Anastomosis, but their application increase the intraoperative time, morbidity and mortality. The use of a self-expanding metal stent (SEMS), in the first time, can enhance the feasibility of laparoscopic colectomy, avoiding the need for a colostomy and offering the advantages of a combination of two minimally invasive procedures.

Method: Between 2003 and 2008, an SEMS was placed in 39 cases of left colon obstruction, being the obstruction successfully resolved in each case. Eight patients were approached by laparoscopy to attempt the definitive colectomy. We evaluated the location and characteristics of the obstruction, effectiveness and complications of SEMS insertion, time interval between the insertion of SEMS and laparoscopic surgery, and postoperative data.

Results: The tumors were situated in the recto-sigma (1 case), sigma (5 cases) and descending colon (2 cases). Immediate relief of the obstruction was achieved in all cases after SEMS insertion of the stent, however in a case, we observed the migration of stent on 11th day after placement of SEMS. The 8 patients were operated on an average of 14 days (range 6-20) after insertion of the stent. Conversion to open surgery was necessary in one case for reasons not related to the stent.

Conclusion: Results of the combination of SEMS and elective laparoscopic surgery demonstrate that the procedure is feasible as a bridge to surgery in the management of obstruction left-sided colon. However, in those oncologic cases, it is unclear what results of the procedure associated with oncologic outcomes.

P.115 PREDICTION OF RESPONSE TO NEO-ADJUVANT RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER BY MEANS OF SEQUENTIAL 18F-FDG-PET
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Introduction: The current approach to curative treatment of locally advanced rectal cancer is comprised of surgery combined with neo-adjuvant (chemo)radiotherapy. Radiosensitivity of rectal cancer however is variable. Morphological imaging techniques are performing poorly in assessing the response because of their inability to differentiate residual neoplastic from scar tissue. The aim of this study was to investigate the potential of sequential 18F-FDG-PET/CT in assessing the response of rectal cancer to neo-adjuvant radiotherapy (RT), and to determine which parameter(s) can be used as useful metabolic response indices.

Method: Patients (pts) were treated by Tomotherapy: dose of 46 Gy to the presacral space and integrated boost to 55.2 Gy on the tumor, if circumferential resection margin was < 2 mm on magnetic resonance imaging. Pts underwent total mesorectal excision within 6 w after completion of RT, and tumor regression was graded histologically. 18F-FDG-PET or PET/CT scans were acquired prior to and in the 5 weeks after the end of RT.

Tumoral uptake of 18F-FDG was assessed semi-quantitatively using standardized uptake values (SUV). The percentage difference (A) between pre- and post RT scans in SUV(max, SUV(mean, average SUV of tumoral pixels with SUV > 2.5) metabolic volume (MV, sum of tumor pixels with SUV > 2.5) and the total glycolytic volume (GVG, MV x SUV(mean)) was investigated as possible metabolic response indices.

Results: 45 consecutive pts (34 male and 11 female; age 65.4 ± 12.5) with histologically confirmed rectal adenocarcinoma (cT3cT4) were enrolled. Following neo-adjuvant RT, of the 45 pts 20 (44.4%) were classified as responders, while the remaining 25 (55.6%) were non-responders. Intense 18F-FDG uptake was seen in all tumors prior to neo-adjuvant RT. Average SUV(max) was 12.9 ± 2.6 (no significant different between responders and non-responders). When classifying pts according to histologic significant differences in average ASUV(max) (55.8% vs 37.4% decline, p=0.023) and ASUV(mean) (40.1% vs 21.9%, p=0.001) between responders and non-responders respectively were observed. For MV and GVG decreases were more prominent in responders (72.9% vs 62.7% and 80.2% vs 68.1%, respectively), but not significantly different from non-responders.

Conclusion: Sequential FDG-PET/CT is a useful method to evaluate response of rectal cancer to neo-adjuvant RT. ASUV(max) and ASUV(mean) are parameters that can be used as indices of metabolic response.

P.116 POPULATION BASED SURVIVAL OF PATIENTS SUFFERING FROM PERITONEAL CARCINOMATOSIS DOES NOT IMPROVE OVER TIME DESPITE INCREASING USAGE OF PALLIATIVE CHEMOTHERAPY
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Objectives: Several trials have shown that treatment with palliative chemotherapy improves median survival of patients suffering from metastasised colorectal cancer. It remains unclear however whether these results also apply to patients suffering from peritoneal carcinomatosis (PC). As modern imaging techniques often fail to detect PC, these patients are rarely included in randomised trials, being classified as having nonmeasurable disease. Therefore, there is a lack of data considering effectiveness of modern chemotherapy treatment in this subgroup of patients. Aim of this study was to provide data on use and effectiveness of chemotherapy in unscreened patients with PC. We therefore analyzed population-based survival data of patients who presented with synchronous PC from colorectal origin.

Method: All patients with synchronous PC of colorectal origin diagnosed in the registration area of the Eindhoven based Cancer Registry from 1995 to 2008 were included. Date of diagnosis was divided into two periods (1995-2000 and 2001-2006) according to the availability of chemotherapy for metastastic colon cancer. We assessed overall survival according to period. Follow-up was complete until December 31st, 2007.

Results: In total 815 patients with synchronous PC were diagnosed. Chemotherapy use gradually increased over time from 15% in 1995 to 42% in 2006 (p=0.01) for all ages. Chemotherapy usage was higher in patients aged <70 years, increasing from 25% in 1995 to 64% in 2006 (p<0.001). Median survival for patients diagnosed with PC only in 1995-2000 was 35 weeks [95% confidence interval (CI) 26-41], while patients diagnosed in 2001-2006 had a median survival of 36 weeks (95% CI 17-42). Median survival for patients diagnosed with PC plus other metastases in 1995-2000 was 20 weeks (95% CI 15-27), while patients diagnosed in 2001-2006 had a median survival of 24 weeks (95% CI 19-29). To compare these figures with median survival for unscreened patients with synchronous metastases restricted to the liver: this increased in the same area and time frame from 34 weeks [95% CI 29-39] to 51 weeks [95% CI 43-57].

Conclusion: Despite the increasing usage of palliative chemotherapy and the availability of more potent agents the population based survival of patients with PC has not improved over time. These data suggest that palliative chemotherapy is not effective in prolonging survival in patients with PC, in contrast to the results reported from patients with other sites of metastasis. Treatment by Hyperthermic Intraperitoneal Chemotherapy (HIPEC), which has shown promising results in selected patients, may provide an interesting alternative.

P.117 HYPERTERM INTRAPERITONEAL CHEMOTHERAPY IMPROVES SURVIVAL AFTER CYTOREDUCTION SURGERY FOR PERITONEAL CARCINOMATOSIS IN THE RAT
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Objectives: The combination of cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has recently been introduced as a treatment strategy for selected patients with peritoneal carcinomatosis from colorectal origin. It remains unclear however whether the addition of hyperterm chemotherapy is essential to achieve the reported survival benefit. As this and many other questions concerning HIPEC techniques cannot be answered in clinical trials, the availability of an animal model is required for future research. Aim of this study was to develop an animal model in which cytoreduction and application of HIPEC can be performed, and to unequivocally establish the benefit of HIPEC as adjuvant therapy after cytoreductive surgery for peritoneal carcinomatosis of colorectal origin in rats.

Method: Sixty WAG/Rij rats were inoculated intraperitoneally with the rat colon carcinoma cell line CT-331. Seven days after tumor transfer, median laparotomy was performed in all animals. Animals were randomized into three treatment groups (n = 20 each). Group 1: cytoreductive surgery only, group 2: cytoreductive surgery followed by HIPEC (intraperitoneal lavage at 41°C during 90 minutes) with a dose of mitomycin 15 mg/m2, group 3: cytoreductive surgery followed by HIPEC, dose of mitomycin 35 mg/m2. Survival was the primary outcome parameter. Humane endpoints of the animals were determined by a biotechnician blinded for the different treatment regimens. Maximum follow up was 140 days.

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Results: Median survival of rats treated with cytoreductive surgery was only 43 days. Addition of HIPEC 15 mg/m² and HIPEC 35 mg/m² increased median survival in both groups when compared to the control group, being 80 days (p<0.01) and 100 days (p<0.001), respectively. Perioperative mortality was 5% in each group, related to surgical complications.

Conclusion: An animal model was developed in which cytoreductive surgery and HIPEC can be performed, allowing comparison of survival outcomes between different treatment groups. This model can be used to answer future questions concerning new treatment strategies for peritoneal carcinomatosis.

Furthermore, the addition of HIPEC to cytoreductive surgery prolongs survival in rats with peritoneal carcinomatosis. This study shows that the reported beneficial effect of the combination therapy is not only a result of the surgical cytoreduction, but that addition of HIPEC to surgical procedures for peritoneal carcinomatosis is essential to achieve the survival benefit reported in clinical studies.

Figure 1.

P.118 RELATIVE SURVIVAL FOR COLORECTAL CANCER PATIENTS BY DUKES' STAGE

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Objectives: Survival from colorectal cancer (CRC) has increased in recent years, but the extent of stage-specific improvement is not known. This study has examined the change in relative survival for colorectal patients in a large population broken down by stage at diagnosis.

Method: The study population consisted of all patients diagnosed with CRC in Scotland 1997-2005. Cancer data were obtained from the Scottish Cancer Registry. Dukes’ stage was not recorded for 19% of patients. To avoid bias in the analysis due to any systematic differences between patients with Dukes’ stage not recorded and the rest of the study population, a 5 fold multiple imputation model was used to generate Dukes’ stage, where missing. This used the values, from all patients, of year of diagnosis, site, status, survival time, surgery, radiotherapy and chemotherapy treatment, age and socioeconomic deprivation. Relative survival was used in order to examine the survival directly related to colorectal cancer and life tables for the whole of Scotland by age and sex were obtained from the Government Actuary’s Department for 1997 to 2006. Survival was examined at 6 months, 1, 3 and 5 years after diagnosis.

Results: There were 27,426 patients (53.5% male) diagnosed, approximately 3000 each year. The proportion with Dukes’ stage not recorded rose over the period from 14.6% to 22.9%. After imputation, 12% of patients were recorded as Dukes’ A, 30% as Dukes’ B, 28.6% as Dukes’ C and 29.4% as Dukes’ D. Relative survival for the whole study population increased at each time point (from 6 months to 5 years) between 1997 and 2005 with the biggest difference seen for 5 years after diagnosis (50.2% to 55.2%). Examining the data by Dukes’ stage at 6 months after diagnosis showed little difference in survival for Dukes’ A, B or C patients but Dukes’ D showed an increase from 45.7% to 52%. At 1 year there was again little change for Dukes’ A or B patients and an increase in Dukes’ D from 29.8% to 36.3%. However Dukes’ C patients now showed a steady rise in survival over the period from 76.8% to 84.9%. A modest increase for survival was seen for Dukes’ A, B and D at 3 years but again a steady increase for Dukes’ C from 54.1% for those diagnosed in 1997 to 65.5% for those diagnosed in 2004. This pattern in survival for Dukes’ stage was repeated at 5 years after diagnosis with Dukes’ C patients having an increase in survival from 44.5% to 57.6% in the period of diagnosis 1997 to 2002.

Conclusion: The largest increases in relative survival were seen in patients diagnosed at Dukes’ C and this was particularly noticeable at 3 and 5 years after diagnosis. Using multiple imputation enabled survival for CRC to be examined by Dukes stage without any potential bias arising from complete case analysis and has provided the first analysis of the widely observed improvement in colorectal cancer survival broken down by stage at diagnosis.

P.119 LARGE AGE AND HOSPITAL DEPENDENT VARIATION IN ADMINISTRATION OF ADJUVANT CHEMOTHERAPY FOR STAGE III COLON CANCER IN SOUTHERN NETHERLANDS

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Background: The purpose was to assess factors associated with the administration of chemotherapy and their relation to survival at a population-based level.

Patients and method: All patients diagnosed with primary colon cancer stage III from 2001 to 2007 in the area of the Eindhoven Cancer Registry were included (n=1,637). We examined determinants of the administration of adjuvant chemotherapy and their relation to survival.

Results: The proportion of patients receiving adjuvant chemotherapy decreased with increasing age from 85% for patients <65 yr to 68% for those 65-74 yr and 17% for patients ≥75 yr, with large inter-hospital variation. Elderly patients (odds ratio(OR)0.1(95%confidence interval(CI) 0.1-0.1)) and those with comorbidity(OR=0.695%CI 0.5-0.8) received adjuvant chemotherapy less often. Patients with an intermediate(OR=495%CI 1.1-1.9) or high socio-economic status(OR=1.595%CI 1.2-2.0) or stage III(OR=1.595%CI 1.2-2.0)) received adjuvant chemotherapy more often. Adjuvant chemotherapy was the most important predictor of survival. In a multivariable analysis, older age was no longer a significant negative predictor of survival, in contrast to comorbidity, higher tumour stage, poor tumour grade, and male gender. The improvement in survival between 2001 and 2006 did not reach statistical significance.

Conclusion: Adherence to guidelines for adjuvant chemotherapy was still suboptimal in 2007, especially for elderly patients, and differed widely between hospitals.
P.120 IMPROVED SURVIVAL OF COLON CANCER DUE TO ADVANCES IN MANAGEMENT; A NATIONWIDE POPULATION-BASED STUDY IN THE NETHERLANDS 1989-2006

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Aim: The aim of this study was to describe changes in treatment of colon cancer over time and the influence of these changes on survival in the The Netherlands, in the period 1989-2006.

Method: All patients from the Netherlands Cancer Registry with invasive colon cancer diagnosed in the period 1989-2006 were included (n=103,744). Trends in treatment over time were analysed. Relative survival and estimated annual percentage changes (EAPC) were calculated. Multivariable relative survival analyses were performed to estimate relative excess risk (RER) of dying.

Results: The use of adjuvant chemotherapy in patients <75 years with stage III disease increased from 19% in 1989-1993 to 79% in 2004-2006 (p<0.0001) and from 1% to 19% in patients 75+ years with stage III disease in the same period (p<0.0001). In stage II disease patients <75 years the use of adjuvant chemotherapy increased from 4% in 1989-1993 to 10% in 2004-2006, while almost none of the 75+ years patients received this treatment. Resection rates remained stable over time at 98% for stage I-III colon cancer patients. In stage IV colon cancer patients resection rates of the primary tumour decreased from 72% to 63% in those <75 years, while chemotherapy administration increased from 23% to 64% in those <75 years between 1989-1993 and 2004-2006. Survival of patient with colon cancer increased over time from 52% in 1989-1993 to 58% in 2004-2006 (EAPC: 0.38 (95% CI: 0.21-0.56)) among males and from 55% to 58% in the same period among females (EAPC: 0.18 (95%CI: 0.04-0.32)). The largest improvement in survival could be noted among stage III disease patients, with patients treated with adjuvant chemotherapy exhibiting a RER of 0.41 (95% CI: 0.39-0.44). Among stage IV patients, metastasectomy (RER 0.31 (95%CI 0.28-0.35), resection of primary tumour (RER 0.36 (95%CI: 0.35-0.38)), and chemotherapy (RER 0.59 (95% CI: 0.57-0.62)) were important prognostic factors.

Conclusion: There were substantial improvements in management and survival of colon cancer between 1989 and 2006. Particularly the use of adjuvant chemotherapy increased steeply in stage III patients with colon cancer; this group of patients experienced the largest improvement in survival.

P.121 QUALITY MANAGEMENT IN RECTAL CARCINOMA: WHAT IS FEASIBLE?

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Objective: A cohort study was carried out to analyse quality indicators in the diagnosis and treatment of rectal carcinoma.

Method: The German S3 Guidelines for Colorectal Carcinomas formed the basis of this study. In a workshop in Burghausen in 2005 (ArbeitsgruppeWorkflow Rektumkarzinom II), quality indicators for rectal carcinoma were defined and appropriate target values were recommended. Data of 2470 patients with rectal carcinoma treated between 1985 and 2007 at the Department of Surgery, University of Erlangen, were collected prospectively. They were analysed with respect to indicators for process quality of clinical and pathological diagnosis, surgical treatment, and multimodal treatment. In addition surrogate indicators and definite indicators of treatment-outcome quality were investigated. Four time periods (1985-1991 (n=828), 1992-1997 (n=595), 1998-2003 (n=608), and 2004-2007 (n=439)) were compared to illustrate the developments in rectal carcinoma treatment and quality management.

Results: Most of the indicators analysed from 2004 to 2007 fulfilled the defined target values and will be discussed. The indicators of process quality of surgical treatment and the surrogate indicators of outcome quality in surgery showed excellent results. Comparing this to previous data, it displays the new developments such as introduction of multimodal treatment for high-risk patients. While the rate of locoregional recurrences decreased, no significant improvement in survival was found.

Conclusion: Careful analysis of quality indicators is important for both quality management and comparison of treatment results. The progress in diagnosis and treatment requires a continuous update of definitions and target values.

P.122 COMPRESSION ANASTOMOSIS USING AKA-2 DEVICE IN RECTAL CANCER PATIENTS

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Objective: The aim of this study is to investigate safety of compression anastomosis (AKA-2) in rectal cancer patients undergoing surgical and combined treatment.

Method: 283 rectal cancer patients, who underwent anterior resection of the rectum in the department of oncoproctology of Russian Cancer Research Center during 2002-2009 with compression anastomosis (AKA-2) were included in the trial. Tumors were localized from 7 to 15 cm above anal verge. 176 patients (62,6%) had rectum cancer, 90 patients (31,8%) had upper rectal cancer, 91 patients (28,6%) had middle rectal cancer, 4 patients (1,4%) had low rectal cancer. 176 patients (62,6%) underwent surgical treatment, the rest 107 patients (37,4%) had different types of combined treatment. Tumor stage distribution was as follows: stage I - 44 (15,5%), stage II - 121 (42,8%), stage III - 64 (22,6%), stage IV - 54 (19,1%).

Results: Anastomotic leakage rate was 8,8% (25 patients). Among them 10 (40%) were symptomatic and required a colostomy. Anastomotic leakage was more commonly observed in tumors localized low in the rectum: 16% for middle ampullar, 6,6% for upper ampullar and 3,7% for rectosigmoidal tumors. With regard to treatment type anastomotic leakage rate was 10,7% (19 patients) in surgical treatment group and 5,6% (6 patients) in combined treatment group. No lethal cases were observed.

Conclusion: Combined treatment does not increase the anastomotic leakage rate. Low localization of anastomosis in the rectum is the main adverse prognostic factor for anastomotic leakage, which requires reconsideration of surgical tactics for low rectal tumors. Compression anastomosis (AKA-2) is safe and can be recommended for rectal cancer surgery.

P.123 FAILURE OF SYSTEMIC TREATMENT IN PATIENTS WITH PERITONEAL CARCINOMATOSIS FROM COLORECTAL ORIGIN

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Objective: Approximately 3% of patients suffering from colorectal cancer present with synchronous peritoneal carcinomatosis. Systemic chemotherapy treatment has been shown to be effective in patients with stage IV colorectal cancer. However, recent data showed that population based survival of patients with PC does not increase over time despite an increasing availability and usage of systemic

Figure 1. Trends in adjuvant chemotherapy use.
CHEMORADIATION RESPONSE MONITORING IN LOCALLY ADVANCED RECTAL CANCER: ROLE OF 18F-FDG PET

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Objective: Molecular imaging with 18F-FDG-PET already plays a pivotal role in staging before surgical resection of locally recurrent cancer and metastases. However, to date no clinical or image marker has been identified for tumor response predictor to chemoradiotherapy (CRT) in locally advanced rectal cancer. We examine the role of positron emission tomography for monitoring and predicting response after CRT.

Method: 43 patients with locally advanced rectal cancer and without distal disease were prospectively studied. CRT was performed in our institution. Surgery was accomplished 8 weeks after the completion of CRT. 18F-FDG PET was performed both before and after 6 weeks after completing CRT. Semi-quantitative uptake measurements (SUVmax) were considered for the analysis. The results were correlated with pathological stage of resection according to the Tumor Node Metastasis (TNM) classification. Percentages were calculated with the continuity correction.

Results: Following CRT, 16 patients (37.2%) were responders (10 Grade 1 and 6 Grade 2) and 27 (62.8%) non-responders. Considering all patients, the mean pre-CRT SUVmax was 4.18 (range 0.03-17.4) and 5.18 (range 0.03-17.4) respectively. Furthermore, decrease in percentage was also higher in responders (61.69 vs 57.29% in non-responders).

Conclusion: This study shows that the response rate to systemic chemotherapy is low in patients suffering from peritoneal carcinomatosis. Many patients are unable to complete their intended treatment due to unacceptable toxicity and progression. Treatment by Hyperthermic Intraperitoneal Chemotherapy (HIPEC), which has shown promising results in selected patients, may provide an interesting alternative.

P.126 COMPARISON OF RELATIVE SURVIVAL IN RIGHT- AND LEFT-SIDED ADENOCARCINOMA OF THE COLON IN A NATIONAL COHORT STUDY

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Objective: To analyze changes in survival for right and left-sided colon cancer operated with curative intent over a 10 years period in a national cohort.

Method: All patients in Norway diagnosed with adenocarcinoma of the colon and rectum between 1994 and 2003 were identified from the Cancer Registry of Norway and the Norwegian Rectal Cancer registry. Colon cancers were defined as cancers occurring >15 cm from the anal verge. Appendiceal, coecum, ascending colon and proximal 2/3 of transverse colon were registered as right colon. The distal third of transverse colon, left flexur, descending colon, sigmoid and the rectosigmoid junction were registered as left colon. Five year relative survival was calculated to compare the early and late years of the study period with regard to age, stage and localisation.

Results: The study included 13,020 patients operated with curative intent without distant metastases. The 5-year relative survival for all patients increased significantly from 74% to 77% (p=0.05) from period 1 to period 2. Survival did not change for right colon (73% vs 76%), nor for left colon (74% vs 77%). No significant stage-dependent change in local disease was found, but significantly increased survival in period 2 for regional disease compared to both right and left colon. In patients with regional disease < 75 years, relative survival increased significantly in period 2 for left colon as compared to right colon (70% vs. 62%; p=0.005). For patients over 75 years there was no difference in relative survival (49% vs 46%, p=0.34).

Conclusion: Patients <75 years with left-sided colon cancer with lymph node metastases had a significantly increased survival compared with right-sided colon cancer in the latter study period. This may be due to different sensitivity to adjuvant chemotherapy.
P.127 THE SURGICAL OUTCOME IN PATIENTS WITH LOW- AND MIDRECTAL CANCER OPERATED ON BETWEEN 1998-2007 IN A HIGH VOLUME HOSPITAL IN FINLAND

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Objectives: Much effort has been made to improve the outcome of patients with rectal cancer. Total mesorectal excision (TME) is now the standard surgical method. TME combined with preoperative (chemo)radiotherapy reduces local recurrence rate to 6% versus 11% after surgery alone. Centralization of rectal cancer surgery to experienced units has further improved the outcome. The aim of this study was to assess the surgical outcome in a high volume hospital in Finland after combined modality treatment for low and midrectal cancers.

Method: TME technique was routinely used during the study period 1999-2007. Laparoscopic operations were started in 2001. Patients with midrectal T3 tumours received a short course PRT followed by a resection within a week. Long course CRT was used in fixed T3/T4 tumours and in low T3 tumours requiring APR. Adjuvant postoperative chemotherapy was used in stage III disease. Follow-up information (mortality, morbidity, re-operation rate, local recurrence rate and survival) was collected on a prospective database.

Results: Altogether 179 patients aged median 68 (range 38-87) years, were operated on for low- or midrectal cancer (AR 121, APR 50, proctocolectomy 5). Fourteen of the 65 patients (21.5%) with tumours at or below 6 cm underwent anterior resection. Short-course PRT was given to 65 (36%) patients and long-course chemoradiotherapy to 67 (37%) patients. The postoperative mortality was 2.2% (3.7% after conventional surgery, 1% after laparoscopic surgery) and morbidity 39.7% (33% after laparoscopic and 48% after open surgery). The re-operation rate was 7.3% (13 of 179 patients); 10% after conventional surgery and 5% after laparoscopic surgery. Nineteen patients (11%) had an anastomotic leak (all staple lines). Of the 179 patients, 166 (93%) were operated on with curative intent (R0-resection). The operation was considered non-curative, if the patient had distant metastases or the circumferential resection margin was less than 1 mm. After a median follow-up time of 4.3 years, the local recurrence rate at five years for all 179 patients was 2.4% after AR and 12.3% after APR (p = 0.008) and for those having R0-resection (n=166) 5.8%: 2.4% after AR and 10.8% after APR. Of the 179 procedures, 100 (56%) were done using laparoscopic technique (68 AR, 32 APR) with no difference in local (5.7% vs. 7.1%, p = 0.7) or distant recurrence rate (24% vs 18%, p = 0.5) between laparoscopic or open surgery. The overall and disease free 5-year survival time for R0-patients was 71.4% and 76.6%, respectively.

Conclusion: The current international standards of care have been well met in this series of patients treated with combined modality therapy. Mortality, re-operation and local recurrence rates are low. However, APR still carries a greater risk for local recurrence than AR. A wide excision to achieve better circumferential resection margin and preoperative CRT may have an essential role in preventing recurrence after APR.

P.128 THE EFFECT OF NEOADJUVANT THERAPY ON ANASTOMOTIC LEAKAGE AND POSTOPERATIVE MORTALITY IN RECTAL CANCER

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Objectives: Neoadjuvant therapies have proven to increase local control in a selection of rectal cancer patients. Potential disadvantages, however, include an increased postoperative complication rate, affecting mortality and long-term quality of life. Aim of this study was to evaluate the number of anastomotic leakages and the postoperative mortality. The postoperative mortality rate was 1.5% and 3.5% after TAM, alone and 6% and 7% after APR and total mesorectal excision (TME) respectively.

Method: Rectal cancer patients with histologically proven T2-4N0-2M0 disease diagnosed between 2006 and 2008 were included. Patients from 1 radiotherapy referral centre and 6 referring hospitals were evaluated. Anastomotic leakage was defined as any leakage occurring more than 1 mm from the anastomosis in CRT patients is becoming standard practice.

Results: In our study reflecting daily practice, no significant difference was found in postoperative mortality or anastomotic leakage rate (range 8-15%) between TAM alone, short course radiotherapy and chemoradiotherapy. Since all postoperative mortality occurred in the elderly patients, the higher rates in the TAM only group may be explained by the overrepresentation of elderly patients in this group. Protecting the anastomosis in CRT patients is becoming standard practice.

Conclusion: The treatment response to chemoradiotherapy (CRT) of locally advanced rectal cancer is known to be very heterogeneous between patients. Thus, an accurate prediction of the individual tumor response already early during CRT could enable response-guided modifications of the treatment protocol. This might help to improve the clinical outcome and to improve the chances for the patient of being considered for a less invasive surgical intervention. Thus, this study was undertaken to develop an accurate prediction model based on clinical and PET variables which could be clinically used as decision support for individualized treatment modifications. Data were prospectively collected at 3 different institutions. Three different imaging time points were analyzed for their predictive value: pre-CRT, during CRT and after CRT, just before surgery.

Method: The datasets with both clinical and imaging variables from 3 different institutions were merged to have a statistical weight. A total of more than 80 patients were treated with long-term chemoradiotherapy (CRT). For all patients, three PET-CT scans were acquired (before CRT, during CRT, after CRT just before surgery). Clinical variables included age, sex, WHO performance status, BMI, cTNM stage. For PET-analyses, the tumors were semi-automatically contoured. Imaging variables consisted of tumor dimensions (GTV, maximal diameter, distance from anal verge) and metabolic activity (SUVmean, SUVmax). In addition, for the follow-up PET scans, all relative differences (response indices, RI) were also included in the evaluation. Multivariate analysis was performed with a 2-norm support vector machine (SVM). Performance of the model was expressed as the area-under-the-curve (AUC) of the receiver-operating-characteristic (ROC) curves and assessed with leave-one-out (LOO) cross-validation. Also, all output was converted to nomograms.

Results: For 23% and 24% of the patients, CRT resulted in a pathologic complete response or near complete response, respectively. Based on the AUCs (Mean +/- SD) of the ROC-curves, the model containing PET variables during treatment reached the highest training performance (0.82+/-0.07) when compared to pretreatment (0.75+/-0.08) and post-surgical (0.72+/-0.10) models. For PET-imaging during treatment, these variables were predictive (ranked by their importance): response index of SUVmax during CRT (0.28), cT-stage (-0.22), cN-stage (-0.18), tumor length (-0.14). The post-CRT PET-based model resulted in lower performance due to a high percentage of inflammatory cases.

Conclusion: The prediction of tumor response based on both clinical variables and PET variables assessed early during treatment was found to be most accurate based on the multivariate analysis. Easy to use nomograms will be presented. A prospective validation of the model is currently ongoing and the next step will be to use the validated model to select patients for treatment modifications.

P.129 A NOVEL NOMOGRAM BASED ON CLINICAL AND PET VARIABLES TO ACCURATELY PREDICT RESPONSE TO RADIOCHEMOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER: TOWARDS INDIVIDUALIZED TREATMENT


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Purpose: The treatment response to chemoradiotherapy (CRT) of locally advanced rectal cancer is known to be very heterogeneous between patients. Thus, an accurate prediction of the individual tumor response already early during CRT could enable response-guided modifications of the treatment protocol. This might help to improve the clinical outcome and to improve the chances for the patient of being considered for a less invasive surgical intervention. Thus, this study was undertaken to develop an accurate prediction model based on clinical and PET variables which could be clinically used as decision support for individualized treatment modifications. Data were prospectively collected at 3 different institutions. Three different imaging time points were analyzed for their predictive value: pre-CRT, during CRT and after CRT, just before surgery.

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Conclusion: The prediction of tumor response based on both clinical variables and PET variables assessed early during treatment was found to be most accurate based on the multivariate analysis. Easy to use nomograms will be presented. A prospective validation of the model is currently ongoing and the next step will be to use the validated model to select patients for treatment modifications.
The potential benefit from CTV reduction in terms of small bowel dose was possible CTV reduction was determined for patients without primary nodal involvement by comparing the recurrences between the RT and the no-RT group. The potential benefit from CTV reduction in terms of small bowel dose was determined by a planning study using both conventional- and intensity modulated radiotherapy (IMRT) on a dataset of 8 patients.

Results: The use of preoperative RT mainly reduces anatomic, lateral and perineal recurrences (Figure 1). In patients without primary nodal involvement only one recurrence was found cranially of the S2-S3 inter-space. This patient was treated with pre-operative RT, and only 3 lymph nodes were examined during pathology. For primary node positive disease, 3 recurrences were located above the S2-S3 inter-space. A reduction of the CTV border cranially to primary node positive disease, 3 recurrences were located above the S2-S3 inter-space. This patient was treated with pre-operative RT on patterns of local recurrences was evaluated. Subsequently, possible CTV reduction was determined for patients without primary nodal involvement by comparing the recurrences between the RT and the no-RT group.

Conclusion: The cranial border of the CTV can safely be lowered to the S2-S3 inter-space for patients without nodal involvement, yielding a significant reduction of dose to the small bowel. As a consequence, a significant reduction of acute and late toxicity can be expected.

Figure 1. Overview of the recurrence locations for the TME alone (left) and the RT+TME patients (right) stratified for nodal involvement, N0 (lime), N+ (red) in an anterior-left sagittal (bottom) view. The purple plane indicates the level of the S2-S3 inter-space.
Method: Antiproliferative activity of AEE788 and/or Celecoxib on colon cancer cell line HT-29 was determined by cell proliferation assay. Effect of these drugs on morphology was also analysed by phase contrast microscopy (20X). Further, extent of cell apoptosis was determined by cell cycle analysis after the treatment with AEE788 and/or Celecoxib for 48hr. To corroborate the cell cycle analysis results, DNA fragmentation analysis was also performed by DNA laddering assay.

Results: The study results showed that AEE788 and/or Celecoxib displayed dose dependent anticancer activity either alone or in combination on HT-29 cell line. From MTT assay, IC50 of AEE788 and Celecoxib were determined as 4.05M and 98.15M respectively. Also the combined treatment with AEE788 and celecoxib led to synergistic activity on growth inhibition of HT-29. AEE788 and/or Celecoxib displayed increasing growth inhibitory activity with increasing dose concentration. The morphological study using phase contrast microscopy revealed the apoptotic characteristics such as cell shrinkage, membrane blebbing, and rounding in AEE788 and celecoxib treatment groups with respect to control HCT 15. Further, the combination treatment of AEE788 and celecoxib displayed remarkable changes in morphology and detachment of cells from the substratum. The apoptotic effect was prominent in combination treatment than either drug alone. In cell cycle analysis, individual drugs exerted dose dependent increase in apoptotic subG0 level. In combination treatment, AEE788 increased the celecoxib induced apoptosis. The apoptosis was prominent in combination treatment than the individual drug used in the study. Celecoxib alone or in combination with AEE788 treatment resulted into internucleosomal cleavage. AEE788 alone did not induce the DNA fragmentation.

Conclusion: To the best of our knowledge, this is the first study signifying the combination treatment of AEE788 and celecoxib on colon cancer cell. The study signifies the synergistic antiproliferative activity in the combination treatment. Combination treatment using AEE788 and celecoxib leads to apoptosis of colon cancer cell line. The mechanism underlying the synergistic or additive activity appears to enhancement of apoptosis and G1 phase arrest. These results justify the further investigation of the combination AEE788 and celecoxib on colon cancer cell. Thus, combined treatment of AEE788 and Celecoxib could be an additive and novel approach for the inhibition of growth of the malignant colon cancer.

P.132 Figure 1. Morphology of AEE788 and/or celecoxib treated HT29.

P.132 Figure 2. Cell cycle analysis of drug treated HT29.
P.134 MARKED IMPROVEMENTS IN SURVIVAL OF PATIENTS WITH STAGE II-IV RECTAL CANCER IN THE NETHERLANDS 1989-2006: AN ANALYSIS OF CHANGES IN TREATMENT AND SURVIVAL


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Objectives: Since the 1990s, treatment of patients with rectal cancer has changed in the Netherlands. The aim of this study was to describe the implementation of these changes in treatment over time and evaluate the effects of these changes on survival.

Method: From the Netherlands Cancer Registry all patients with invasive primary rectal cancer diagnosed during the period 1989-2006 were selected. The Cochran-Armitage trend test was used to analyze trends in treatment over time. Relative survival and mean annual percentage changes were calculated to quantify survival trends. Multivariate relative survival analyses were performed to estimate relative excess risk (RER) of dying.

Results: In total, 40,888 patients were diagnosed with rectal cancer during the period 1989-2006. The resection rate decreased, particularly in patients aged 75 years or older. The proportion of patients with stages II and III receiving preoperative radiotherapy increased to 68% in younger patients (<75 years) and to 51% in older patients (>75 years) in the period 2004-2006, whereas the use of postoperative radiotherapy decreased. Neoadjuvant chemoradiation was introduced for patients with locally advanced stages II and III disease. The administration of chemotherapy in patients with stage IV increased over time to 66% in younger patients (<75 years) and to 29% in older patients (>75 years) in the period 2004-2006. The proportion of patients with stage IV disease who underwent a resection of the primary tumour decreased in the period 2004-2006 to 44% in younger patients (<75 years) and to 28% in older patients, whereas the proportion of patients younger than 75 years who underwent a metastectomy slightly increased from 1% to 7%. Both in males and in females, five-year relative survival increased toward 60% and 59%. The highest increase in survival was seen in patients with stage III disease. In the multivariate analyses the risk of dying improved over time for patients with stages II-IV. Both patients with preoperative radiotherapy and patients with postoperative radiotherapy had a lower risk of dying compared to patients without radiotherapy (RER 0.51 (95% CI 0.44-0.59) and RER 0.75 (95% CI 0.64-0.89) respectively) in patients with stage II disease. Preoperative radiotherapy and adjuvant chemotherapy were important prognostic factors in stage III patients. For stage IV disease, patients who underwent a resection of the primary tumour (RER 0.42 (95% CI 0.40-0.45), who underwent a metastectomy (RER 0.38 (95% CI 0.31-0.46) and who received chemotherapy (RER 0.62 (95% CI 0.58-0.66) had a lower risk of dying.

Conclusion: The improvements in therapy for rectal cancer have led to increased survival. Patients with stage III disease experienced the largest improvement in survival.

P.135 THE EFFECT OF SHORT-COURSE PREOPERATIVE IRRADIATION ON LOCAL RECURRENCE RATE AND 5-YEAR SURVIVAL IN RECTAL CANCER: A POPULATION-BASED NATIONAL STUDY

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Objectives: Approximately 50% of all patients in Sweden with rectal cancer receive preoperative irradiation (RT). The aim of the study was to evaluate the effect of preoperative RT with 3x5 Gy on local recurrence and 5-year survival on tumours in different levels from the anal verge.

Method: All newly diagnosed rectal cancers in Sweden are reported to the Swedish Rectal Cancer Registry (SRCR). Between 1995 and 2001, 6878 patients (stage I-III) were operated on with an anterior resection (AR), abdominoperineal-resection (APR) or with a Hartmanns procedure (HA). Among those patients 3282 (48%) had no irradiation and 2808 (41%) had received preoperative short-course irradiation. To reduce the influence of referral bias, patients operated on with a HA or older than 75 years were excluded when 5-year survival was analyzed (n=3466). Data was analyzed according to age, gender, stage and tumour height (0-5 cm, 6-10 cm, 11-15 cm).

Results: The overall local recurrence rate was 7.7 %. After adjustments for age, gender and stage pre-operative RT gave significantly lower local recurrence rates on all heights, (relative risk 0.42 (0.30-0.60)). See Table.

Table

<table>
<thead>
<tr>
<th>Local recurrence</th>
<th>RT+</th>
<th>RT-</th>
<th>Rel. difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 cm</td>
<td>7.5%</td>
<td>11.6%</td>
<td>37%</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>6-10 cm</td>
<td>4.9%</td>
<td>9.2%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>11-15 cm</td>
<td>3.8%</td>
<td>8.4%</td>
<td>55%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 1</td>
<td>1.6%</td>
<td>3.3%</td>
<td>52%</td>
<td>&lt;0.021</td>
</tr>
<tr>
<td>Stage 2</td>
<td>4.3%</td>
<td>9.0%</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 3</td>
<td>9.5%</td>
<td>15.0%</td>
<td>37%</td>
<td>&lt;0.001</td>
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</table>

The overall 5-year survival was 59%. Among patients <76 year and operated on with an AR or APR the 5-year survival was 70%. A significant survival benefit after RT was only found in a subgroup of patients with low tumours in stage III (p<0.001).

Conclusion: In contrast to the Dutch TME study this population-based study shows a significant effect of pre-operative short-course RT on local recurrence rates, independent of tumour height and stage. Data also suggest an effect on 5-year survival in patients with low tumours (0-5 cm) and nodal metastases.
ELDERLY PATIENTS WITH LOCALLY ADVANCEDRECTAL CANCER DO NOT BENEFIT FROM NEOADJUVANT RADIO (-CHEMO) THERAPY

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¹Catharina-hospital Eindhoven, Eindhoven, The Netherlands; ²Comprehensive Cancer Center, Eindhoven, The Netherlands

Introduction: Postoperative mortality rate is increased in elderly rectal cancer patients and this effect persists until six month after the surgery. Age itself, toxicity of the treatment and comorbid conditions contribute to this raised probability of dying from cancer treatment. Treatment principles that apply to the whole group of rectal cancer patients may be different for elderly. The principle of downsizing and downstaging for locally advanced rectal cancer with neoadjuvant radio (-chemotherapy) was tested in a group of patients fit to undergo major surgery.

Patients and method: In a group of 426 locally advanced non metastasized rectal cancer patients, the upper age quartile (older than 70 years n= 101) was compared to the younger patients. All patients had MRI diagnosed T4 or T3d (involved or threatened margins less than 2 millimetres) tumours. In the whole group it had been demonstrated that response to neo adjuvant treatment was related directly to a better oncological outcome. Therefore, response to neoadjuvant treatment and subsequent outcome in elderly was studied.

Results: Six month mortality rate in the different age quartile were: 4.7% in the group younger than 56, 3.3 % in the group aged 56 - 63, 6.1 % in the group aged 64 - 70, and 13.9 % in patients older than 70 years. Response to neoadjuvant treatment was slightly less in elderly patients: 47% were judged non-responders (no lowering of preoperative T-stage), compared to 39% of non responders in the younger patients. Partial response (lowering of one T-stage:i.e. T4-> T3 or T3-> T2) was found in 43% in elderly compared to 42% in younger patients. Excellent response (lowering of two or more T-stages) was found in 10% of the elderly and in 19% of the younger patients. However, unlike in the younger age groups, response did not predict better oncological outcome or survival (except for the 10% excellent responders). Five year overall survival (OS), cancer specific survival (CSS), local recurrence rate (LRR) and metastasis free survival (MFS) of non responders, partial responders and excellent responders were: 30% 40% 100% (p=0.04), 41% 54% 100% (ns), 14% 13% 13% (ns), 63% 57% 100% (ns) respectively. Whereas, in the younger patient groups all the differences were highly significant: OS 49% 64% 81% (p=0.001), CSS 58% 68% 81% (p=0.009), LRR 21% 8% 0% (p=0.001) and MFS 57% 79% 81% (p=0.004) respectively.

Conclusion: This retrospective study demonstrates that treatment related mortality of patients with non metastasized locally advanced rectal cancer is considerable (14%) and is higher than the proportion of patients (10% excellent responders) that potentially benefit from the neoadjuvant treatment. Unlike in younger patients, response does not translate to a better outcome. The biological behaviour seems to be different. Therefore, it is not justified to apply the same treatment principles for younger patients also to older patients.

Figure 1. Kaplan Meier Curve showing effect of magnitude of response to neoadjuvant treatment on OS.

Figure 2. Kaplan Meier Curve showing effect of magnitude of response to neoadjuvant treatment on LRR

Figure 1. Demonstrating the effect of response to neoadjuvant treatment and Local recurrence rate.

Figure 2. Shows that response to neoadjuvant treatment does not seem to be factor in preventing local recurrence in elderly patients.

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P.139 INSULIN-LIKE GROWTH FACTOR 1 (IGF-1) EXPRESSION CORRELATES WITH CLINICAL OUTCOME IN K-RAS WILD TYPE COLORECTAL CANCER PATIENTS TREATED WITH CETUXIMAB-IRINOTECAN


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Introduction: Seventy to 40% of K-RAS wild type colorectal tumors does not seem to benefit from treatment with anti-EGFR monoclonal antibodies. Recent data suggested that in presence of IGF-1 system altered activation colorectal cancer cells might overexpress IGF-1 which could lead to an increased proliferation and resistance to monoclonal antibodies. The interaction between IGF-1 expression and K-RAS mutational analysis was tested in order to verify the ability of IGF-1 to identify a sub-group of patients more likely to benefit from EGFR-targeted antibodies treatment.

Patients and methods: IGF-1 expression and K-RAS mutational status was assessed in advanced colorectal cancer patients receiving irinotecan/ cetuximab.

Results: One hundred and twelve patients were analyzed. IGF-1 was negative in 30 patients (27%) and overexpressed in the remaining 82 cases (73%). In K-RAS negative and IGF-1 positive tumors we observed progressive disease in 9 (30%) and 55 (67%) patients respectively (p = 0.001). Median time to progression was 7.5 months in patients showing IGF-1 negative tumors and 3 months for IGF-1 expressing tumors (p = 0.002). Among K-RAS wild type patients, IGF-1 negative and positive tumors showed a partial response to cetuximab-irinotecan in 13 (65%) and 11 (22%) cases respectively (p = 0.002). Median time to progression in IGF-1 negative tumors was 10 months and 3.2 months in IGF-1 positive colorectal cancers (p = 0.02).

Discussion: IGF-1 proved to be a possible predictive factor for resistance to anti-EGFR monoclonal antibodies in K-RAS wild type colorectal cancer. Combined IGF-1 and K-RAS analysis may represent an effective strategy for a better selection of responding colorectal cancer patients.

P.140 USE OF A MULTIDISCIPLINARY TEAM MODALITY IMPROVES TREATMENT OUTCOMES AND SURVIVAL IN PATIENTS WITH GASTROINTESTINAL CANCER - EXPERIENCE FROM BEIJING CANCER HOSPITAL

J. Gu

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Aim: To address the clinical significance of the multi-disciplinary team (MDT) modality in the treatment of gastrointestinal tumor in China.

Method: Data of patients with gastric cancer and colorectal cancer treated in our center during the past 10 years were collected retrospectively, and was composed of two parts. Part 1: Consecutive difficult cases discussed in the MDT conference from December 2005 to July 2009 (n=581), to investigate the impact of MDT on clinical decision making. Part 2: Consecutive patients with resectable locally advanced rectal cancer from January 2001 to January 2005 (n=265), divided into the MDT group and Control according to whether or not they underwent MDT treatment, to evaluate the prognostic significance of MDT.

Results: The MDT modality runs smoothly in our center, with regular weekly conference and inter-disciplinary consultation. MDT modality caused a considerable proportion of stage changes, including 54.63% (71/205) of rectal cancer, 19.23% (25/130) of colon cancer, and 29.28% (53/181) of gastric cancer; whereas the distant metastasis presented no statistical difference (21.78% vs 22.22%, p=0.993).

Conclusion: MDT modality could significantly influence the strategies of gastrointestinal tumor; patients could benefit from MDT modality in China.
Conclusion: Previous irradiation of the rectum is not associated with a higher incidence of SAEs in these series of metastatic colorectal cancer patients treated with chemotherapy plus bevacizumab with or without cetuximab.

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>Radiotherapy</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Related</td>
<td>41 (27.2%)</td>
<td>205 (35.3%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Unrelated</td>
<td>18 (11.9%)</td>
<td>45 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>no SAE</td>
<td>92 (60.9%)</td>
<td>331 (57.0%)</td>
<td></td>
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Table 1.

SAE in relation to any of the agents

Radiotherapy + N=151 Radiotherapy – N=579

Related 36 (23.8%) 179 (30.9%) 0.07

Unrelated 23 (15.2%) 69 (11.9%) 0.07

no SAE 92 (60.9%) 331 (57.2%) 0.07

SAE in relation to capecitabine and/or oxaliplatin

Radiotherapy + N=151 Radiotherapy – N=579

Related 26 (17.2%) 94 (16.2%) 0.77

Unrelated 33 (21.9%) 154 (26.6%) 0.77

No SAE 92 (60.9%) 331 (57.2%) 0.77

SAE in relation to bevacizumab

Radiotherapy + N=151 Radiotherapy – N=579

Related 26 (17.2%) 94 (16.2%) 0.77

Unrelated 33 (21.9%) 154 (26.6%) 0.77

No SAE 92 (60.9%) 331 (57.2%) 0.77

SAE in relation to cetuximab

Radiotherapy + N=114 Radiotherapy – N=460

Related 6 (5.3%) 44 (9.6%) 0.15

Unrelated 16 (14.0%) 85 (18.5%) 0.15

No SAE 92 (80.7%) 331 (71.9%) 0.15

P.142 CLINICAL AND PATHOLOGICAL FEATURES IN METACHRONOUS VERSUS SYNCHRONOUS METASTATIC COLORECTAL CANCER (CRC)

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Objectives: Approximately 20% of patients have synchronous metastases at the initial diagnosis of CRC, and about 50% of the patients without metastases at presentation will develop metachronous metastases within three years of diagnosis. Conflicting data have been reported on a difference in survival between patients with synchronous versus metachronous metastases. However, few studies compared the clinicopathological data between these two groups. No study has evaluated the differential benefits of chemotherapy in patients with synchronous versus metachronous metastases. The aim of this retrospective study was therefore to investigate the patient demographics and primary tumour characteristics in patients with metachronous versus synchronous metastases, and correlate this with overall survival. For this analysis data were taken from a large randomized multicenter trial in patients with advanced CRC (DCCG CAIRO study, Koopman et al. Lancet 2007).

Method: In the CAIRO study 820 patients were randomized between sequential versus combination treatment with capecitabine, irinotecan and oxaliplatin. For this study formalin-fixed paraffin-embedded material of the primary tumour was obtained from 550 patients. The patient population was divided into two groups based on the time frame within which the metastases were diagnosed. Synchronous disease was defined as distant metastases occurring within, and metachronous disease beyond six months of the primary diagnosis of CRC. Since patients with synchronous metastases without resection of their primary tumour may reflect two populations with different prognosis (i.e. patients in good condition without any symptoms of their primary versus patients in poor condition that does not allow surgery), for optimal comparison we only included patients with synchronous metastases who had undergone a resection of their primary tumour.

Results: Compared to the metachronous group (n=270), patients included in the synchronous group who underwent a resection of the primary tumour (n=280) were younger (p<0.0001), had more often an abnormal serum LDH concentration at randomization (p=0.01), and more often had the liver as the predominant location of metastases (p<0.0001). Revision of the histology from the primary tumour showed that tumours of patients with synchronous disease had larger diameters (p=0.0070), a higher T (p=0.0006) and N stage (p<0.0001), and more frequently a diffuse infiltration pattern (p=0.0199) than patients with metachronous disease. However there was no significant difference in median overall survival between patients with metachronous versus synchronous metastases (18.5 versus 17.6 months, respectively, p=0.24). In a multivariate model the pathological features (T stage p=0.0199), differentiation grade (p=0.0137), classification (p<0.0001) were together with serum LDH at randomization (p=0.0001) independent predictors for overall survival in patients with advanced CRC treated with palliative chemotherapy.

Conclusion: CRC patients with synchronous metastases in whom a resection of the primary tumour was performed had more unfavourable tumour characteristics in comparison to patients with metachronous metastases. However, this does not translate into a difference in overall survival.