treatment following relapse was close to *21,000 in both arms. Total lifetime disease-related costs were *23,129 with oxaliplatin vs. *17,285 with 5-FU/LV. The resulting incremental cost-effectiveness ratio for FOLFOX4 compared to 5-FU/LV was *9,328 per LY gained, after discounting costs and outcomes at 5% per annum.
Conclusions: Adjuvant chemotherapy with FOLFOX4 has shown a significant DFS benefit over 5-FU/LV in the MOSAIC trial. We extrapolated the within-trial data to estimate a 1.34 (−0.01–2.68) year benefit in overall life expectancy in patients with stage III disease. If this benefit is confirmed, we estimate that FOLFOX4 would cost approximately *9,300 per LY gained, which compares favourably with other accepted interventions in oncology.

References

[1] De Gramont, 2005 ASCO Annual Meeting, Abstract 3501

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Phase I/II study of preoperative cetuximab, capecitabine and external beam radiotherapy in patients with locally advanced rectal cancer (LARC)

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Background: Capecitabine is rapidly replacing 5-fluorouracil as the standard agent in colorectal treatment regimens for locally advanced rectal cancer (LARC). Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor. Both agents are active in the treatment of advanced colorectal cancer and have demonstrated radiosensitising properties. The aim of this study was to establish the feasibility of a combination of weekly cetuximab and daily capecitabine with concurrent radiation for patients with LARC. Previous studies have shown that the Recommended Dose of Capecitabine in combination with radiation for LACR is 825 mg/m^2 twice-daily.
Material and Methods: Ten patients with LARC (T3–T4 and/or N+) received radiotherapy (1.8 Gy, 5 days a week over 5 weeks, total dose 45 Gy, 3D conformational technique) in combination with cetuximab (initial dose 400 mg/m^2 given one week before the beginning of radiation followed by 250 mg/m^2/week for 5 weeks) and two different doses of capecitabine for the duration of radiotherapy (including weekends), according to phase I methodology (650 mg/m^2 twice-daily, first dose level; 825 mg/m^2 twice-daily, second dose level). Dose-Limiting Toxicity (DLT) was defined according to Dunst (JCO 2002).
Results: Four and six patients (ECOG 0–1; median age: 62; transrectal ultrasound staging: T3N0: 5, T3N1:3, T4N0:2) were treated at the first and second dose levels of capecitabine, respectively. No DLTs occurred at either capecitabine dose. Radiotherapy was administered as planned to all patients. Adverse event profiles were consistent with the treatments used (grade 1/2 acne-like rash in all patients and grade 1/2 NCI-CTC diarrhea in 7 patients). Grade 3 NCI toxicities were observed in 5 patients (anal pain in 4 and dermatitis in 1). No grade 4 toxicity was recorded.
Conclusions: Preoperative radiotherapy in combination with capecitabine and cetuximab is feasible and well-tolerated for LARC. The recommended Doses for phase II evaluation are Capecitabine 825 mg/m^2 twice-daily without interruption during the duration of radiotherapy and Cetuximab at a loading dose of 400 mg/m^2 followed by 250 mg/m^2/week. The efficacy of this combination to downstage LARC is currently being investigated in a larger phase II study with a total planned accrual of 40 patients.

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Feasibility study of combined preoperative intensity-modulated radiation therapy (PIMRT) with concurrent capecitabine/oxaliplatin in patients with locally advanced rectal cancer (LARC)

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Background: Preoperative 5FU-based chemoradiation is the standard of care in LARC. New chemoradiation regimens based on Capecitabine and Oxaliplatin may enhance downstaging although acute effects may also be increased. IMRT may overcome this radiosensitizing phenomenon by decreasing the size of the PTV with a resultant reduction in the volume of several OAR's.
Material and methods: Patients (pts) with LARC received PIMRT *(step and shoot)* to 47.5 Gy in 19 treatments. Dose was prescribed at the Minimum Tumor Dose of the Gross Tumour Volume (GTV). Daily fractions of 2.5 Gy, 5 days a week were delivered. Capecitabine 825 mg/m^2 bid was given on the radiation days while Oxaliplatin was administered at a dose of 60 mg/m^2 on days 1, 5 and 15. Surgery was planned 4–6 weeks later. We used the RTOG criteria to evaluate acute toxicity. Pathologic response (PR) was analysed using the TNM staging and the scale proposed by the Memorial Sloan-Kettering Cancer Center: Grade 0 (no response), Grade 1 (1–33% PR), Grade 2 (34–66%), Grade 3 (67–95%), Grade 3+ (96–99%), Grade 4 (100%) (*Ruo et al. Ann Surg 2000)*.
Results: A total of 38 pts, 27 males and 11 females with a median age of 61 years, were treated between March 2003 and May 2005. All pt underwent endorectal ultrasound-based staging. Nine pts had T3N0 tumours (24%), 25 pts had T3N+ (66%), 2 pts had T4N0 (5%) and 2 pts had T4N+ (5%). Eighteen tumours (47%) were located in the distal rectum, 15 (39%) in middle rectum and 5 (13%) in the proximal third. Six pts received a lower PIMRT dose as part of an initial feasibility study. All pts except 8 (81%) completed the prescribed treatment; 6 pts did no receive the total dose of chemotherapy and 2 pts did no complete the prescribed radiation dose. Individual toxic events observed included: Diarrhea grade 1–2 (40%), Diarrhea grade 3 (8%), Tenesmus grade 1–2 (71%), Tenesmus grade 3 (13%), Dysuria grade 1–2 (16%) and Leukopenia grade 1–2 (2.5%). Overall, Grade 3 events were seen in 21% of the cases. Downstaging was observed in 20 pts (52%) with PR grade * 3+ in 45% of the specimens (Grade 4: 10%). In addition 21 of 25 initially N+ pts (84%) turned out to be pN0. The sphincter preservation rate for those pts with tumors located in the distal third of the rectum was 44%.
Conclusions: Concurrent Capecitabine/Oxaliplatin-based PIMRT (47.5 Gy/2.5 Gy/19 Rx) is feasible in pts with LARC. Grade 3 acute events are seen in 21% of the patients with an outstanding rate of PR grade * 3+.

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Acute appendicitis as a sign of a colorectal carcinoma

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Background: The concurrence of acute appendicitis and a colorectal carcinoma is well documented; suspicion is therefore raised of such a causal relationship in older patients. However, very few patients with colorectal cancer have had an appendicectomy within 3 years of the cancer diagnosis. There is no definite evidence that large bowel investigation is warranted following an appendicectomy for acute appendicitis in older patients. The aim of this study was to assess acute appendicitis in older patients as a sign of colorectal carcinoma and to investigate if there was a relationship between the two conditions.
Material and Methods: A 9 year retrospective review of all patients aged over 50 years taken to theatre with a presumed diagnosis of acute appendicitis. The study period was December 1995 to December 2004. Patient data was collected from theatre records, histology records and case notes. All inflamed appendices removed at colorectal cancer resections were not included.
Results: There were 1286 patients of all ages with histologically proven acute appendicitis. Of 167 patients older than 50 years taken to theatre, 114 (68%) had appendicitis whilst 53 (32%) had a normal appendix. Of the histologically positive cases, 54% were female and mean age was 65 (50–91) years. None had a synchronous colorectal cancer or other pathology at appendicectomy. Of the 114 positive cases, 31 (26%) had a subsequent large bowel investigation as an outpatient; most of these were requested by a consultant with a colorectal interest. No colorectal lesions were detected in these patients. Only 2/114 (1.8%) patients subsequently

presented with colorectal cancer. Both presented at 26 and 48 months respectively post-appendicitis following an initially normal colonoscopy.
Conclusions: Despite anecdotal evidence, the results of this study fail to show that appendicitis in older patients is a useful predictor of colorectal cancer. This study shows no evidence to support the need for large bowel investigation in patients aged over 50 with acute appendicitis.

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Erlotinib as single agent in 2nd and 3rd line treatment in patients with metastatic colorectal cancer. Results of a two-cohort multicenter phase II trial

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Background: Erlotinib (E, TarcevaTM) is a small molecule tyrosine kinase inhibitor (TKI) targeted against the ErbB1 (EGFR) TK receptor. EGFR-directed antibody treatment has shown efficacy in colorectal cancer, and E and other TKIs have demonstrated clinical activity as single agent in pretreated patients with NSCLC. This trial was conducted to evaluate the efficacy of E as single agent in patients with metastatic colorectal cancer (mCRC).
Methods: Patients (pts.) with mCRC must have previously received either one (cohort 1) or two (cohort 2) 5FU-based chemotherapy regimens, including either irinotecan and/or oxaliplatin. Pts. were treated with E (150 mg/day orally) until disease progression with biweekly toxicity evaluations and 8-weekly tumour assessment.
Results: From Oct 03 to Dec 04, a total of 51 pts. were included, 23 in cohort 1, and 28 in cohort 2, respectively. Median age was 67 years [46–83], median ECOG PS was 1 [0–2]. The treatment was generally very well tolerated without appearance of treatment-related grade 4 toxicity and low rates of treatment-related grade 3 toxicities (detailed information for 39 pts available): diarrhoea 18%, nausea 8%, mucositis 5%, hepatobiliary, muscular and fatigue 1 pt. each. Skin rash was observed in 62% of pts. with grade 3 in 13%.
46 of 51 pts. (5 pending) are available for efficacy analysis so far: PR 4% (2 pts. in cohort 1), SD 28%, resulting in a clinical benefit rate (PR and SD for min. 8 weeks) of 32% with no differences between cohort 1 and 2 respectively. Median duration for disease control (7 pts. ongoing) was 30+ and 32+ [range 7–38+] weeks for both cohorts.
Conclusion: As reported in NSCLC, disease stabilisation can be achieved with E monotherapy in a relevant proportion of pts. No difference between 2nd and 3rd line cohort was observed. Importantly, for the first time in mCRC, partial responses were achieved with a small molecule TKI. Final data including progression free and overall survival will be presented.

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Patterns of failure after TME and neoadjuvant/adjuvant therapy including IORT to the presacral space in patients with locally advanced rectal cancer

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Purpose: Changes in surgical technique (total mesorectal excision, TME) have effectively decreased local recurrence rates in locally advanced rectal carcinoma, however a benefit from pre- or postoperative radio- or radiochemotherapy (RCHT) further exists. The effectiveness of additional IORT has been shown in locally advanced rectal cancer after conservative resection but not yet after TME. We therefore reevaluated our patients treated with radiochemotherapy including intraoperative electron boost (IORT) with special regard to the site of recurrence in order to appraise the effectiveness of intraoperative target definition after TME.
Patients and methods: We analyzed the outcome of 176 patients with rectal cancer (stage I: 10%, stage II: 31%, stage III: 50%, stage IV: 9%) treated with IORT after TME (R0: 161, R+: 15) and pre- or postoperative radiochemotherapy. 151 patients received pre- or postoperative radiotherapy (EBRT) with a median dose of 41.4 Gy. In 135 patients concurrent 5-FU based chemotherapy was administered.
Results: Local failure was observed in 16 patients (9.1%) who did not differ in age or gender from the overall treated group. Incidence of local recurrence positively correlated with tumor stage (stage I: 6%, stage II: 4%, stage III: 10%, stage IV: 24%) and surgical margin involvement (R0: 7%, R+: 27%). Preoperative treatment decreased local failure rate to 5% compared to 10% after postoperative treatment. Local recurrence rate was increased in patients with T4 stage, positive lymph nodes, tumor localisation in the lower third or high grading. Seven patients developed local failure within the presacral space, resulting in a local control rate of 96% inside the IORT fields. Considering EBRT fields, another 6 in-field recurrences were seen: retrovesical (3), in front of the promontorium (2), and anastomosis (1), resulting in a local control of 92.7% inside the EBRT fields.
Conclusion: IORT as part of additional therapy after TME is a highly effective regimen to prevent local failure especially in combination with preoperative RCHT, but despite this the presacral space remains the site of highest risk for local recurrence. Stage III/IV disease, T4-situation, positive lymph nodes, localisation in the lower third, high grading, and incomplete resection seem to predict an increased risk for local failure.

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Continent colostomy, a new technique

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Introduction: Abdomino-perineal resection still remains the best oncologically safe operation for carcinoma of the lower third of the rectum. Use of dynamic myoplasty to create a continent stoma has produced promising results. The aim of the study was to establish and test a new model. This new technique was studied on animals and produced promising results.
Patients and methods: Twenty patients with carcinoma of the lower third of the rectum who underwent abdomino-perineal resection were randomized into a control group 10 patients who underwent colostomy by the classical transrectal technique and 10 patients underwent this new technique in which the rectus abdominis muscle was used for wrapping the distal end of the colon in a 270 degrees and fixing the muscle to the anterior rectus sheath, the resulting defect was closed by using a prosthetic mesh.
The two groups were compared in terms of continence degree and the need to wear colostomy appliance during the day time also they were compared using manometric studied. MRI and defecography.
Results: Use of a distal rectus muscle sling surrounding the stoma by 270 degrees achieved a continent colostomy for solid stool in 13 patients. 1 case had post operative mesh infection necessitating removal of the mesh the mean squeeze pressure was double its value for the rectus abdominis sling group compared to the transrectal group.
Discussion: Use of dynamic myoplasty to create a continent stoma has produced early promising results, but long-term stoma continence still waiting for more evaluation and long term follow up of those patients. In contrast to continent perineal colostomy cont abdominal colostomy is associated with minimal complications.

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Treatment of advanced upper gastrointestinal adenocarcinoma with Capecitabine and concurrent radiation therapy: preliminary experience of the San Antonio Cancer Institute

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Purpose: Assessment of the pathologic response rate and toxicity associated with neoadjuvant chemoradiotherapy Capecitabine (Xeloda) and IMRT in patients with upper gastrointestinal malignancies.
Methods: 16 patients (age 47–86 yrs, median 62; 13 male, 3 female) were treated between 12/03 and 10/04. All patients underwent biopsy with 15/16 (94%) histology confirmed adenocarcinoma and 1 neuroendocrine pancreatic tumor. Disease sites in the study were: pancreas (10), cholangiocarcinoma (3), esophageal (1), colon (1), and gastric (1). Tumor stages were T3 (12/16) or T4 (4/16). Radiotherapy was delivered using serial tomotherapeutic IMRT in 12 pts and conformal RT in 4/16. Mean PTV dose was 54 Gy (range 45–58) delivered at 1.8 to 2.0 Gy per fraction. All patients received concurrent chemotherapy Xeloda 825 mg/m^2 on a bid schedule, including 14/15 pts at 1500 mg BID and 1/15 at 2000 mg BID. Two patients required a decrease from 1500 mg to 1000 mg BID secondary to hand–foot syndrome and GI complications. To reduce hand–foot syndromes 13/16 pts were also treated with vitamin B6 at either 50 mg (6/13 – 46%) or 100 mg (7/13 – 54%) TID scheduled dosing.