

colorectal adenocarcinoma. In adenomas, a shift of migration indicating immunohistochemical alterations from top to the base was observed with less differentiated neoplasias. In addition Ln-5  $\gamma 2$  – positive small blood vessels were detected in the invasion zone of 35% of all carcinomas, indicating a role for Ln-5  $\gamma 2$  in tumour angiogenesis.

**Conclusion:** Our data show a distinct change of Ln-5  $\gamma 2$  immunohistochemical pattern during colorectal adenoma-carcinoma-progression; adenomas with higher risk of malignant transformation or increased invasive potency can be identified by Ln-5  $\gamma 2$  immunohistochemistry.

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#### Chemoradiation with raltitrexed and oxaliplatin in pre-operative treatment of stage II/III resectable rectal cancer: long term results of a phase II studies

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**Background:** The aim of the study is to evaluate the impact of a schedule of neoadjuvant chemoradiation with raltitrexed and oxaliplatin on tumor response and long-term outcome, in patients with locally advanced resectable rectal cancer.

**Materials and methods:** Between July 2001 and November 2002 a total of 30 patients received radiotherapy (50.4 Gy) administered to the posterior pelvis for 5 days/week for 5 weeks. Combination of raltitrexed (3 mg/m<sup>2</sup>) and oxaliplatin (130 mg/m<sup>2</sup>) was administered on days 1, 19, and 38. Six to 8 weeks after the end of chemoradiation patients were re-evaluated and underwent surgery. Adjuvant chemotherapy with 5-FU and leucovorin (Machover regimen) was planned to be delivered in patients with positive nodes (pN+) at pathologic examination.

**Results:** Tumor stage at diagnosis was: T3N0M0, 4 patients; T3N1M0, 17 patients; and T3N2M0, 9 patients. All patients underwent surgery with R0 margins. Sphincter preservation was obtained in 93% of patients. The median follow-up was 47 months (range30–61).

In all resected patients, the pathologic stages observed were: pT0N0M0, 9 patients; pT<sub>mic</sub>N0M0, 6 patients; pT<sub>mic</sub>N1M0, 2 patients; pT2N0M0, 3 patients; pT3N0M0, 6 patients; and pT3N1M0, 4 patients. Overall, tumor downstaging was reported in 20/30 (67%) patients and nodal downstaging in 23/30 (77%) patients with cN1–N2 stage. TRG was evaluated in all patients: TRG1, 9 patients; TRG2, 8 patients; TRG3, 8 patients; TRG4, 4 patients; TRG5, 1 patient. To date all patients are alive; no patients had relapse of local disease; the rate of metastases is 13%, with a median metastases free survival of 41 months, and a 5-years MFS of 86%. Even without any statistical significance, grouping patients according pT0–2 vs pT3, TRG1–2 vs TRG3–5 and pN0 vs pN+, we found a better results in responding patients, with a 5-years MFS of 89% in pT0–2 vs 86.5% in, 87% in TRG 1–2 vs 84% in TRG 3–5, and 86.7% in pN0 respect 83.3% in pN+.

**Conclusions:** Preoperative chemoradiation with novel agents showed an elevated rate of tumor response (57% had pT0 or pT<sub>mic</sub>), with excellent results in terms of OS and LC, in patients with stage II/III rectal cancer. The 5-year MFS was 86%. Lower pT, TRG and pN stages seems to show a correlation with better results. A longer follow-up is required to obtain more stable results.

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#### Surveillance schedules and CEA workup in post operative rectal cancer patients

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**Background:** The follow-up of rectal cancer patients after potentially curative surgery has been shown to vary widely. The optimal schedule for such follow-up remains unknown. This study investigates the relationship between the age of the surgeon and choice of surveillance strategy.

**Methods:** A detailed questionnaire was sent to the 1795 members of the American Society of Colon and Rectal Surgeons (ASCRS) to measure how these specialists conduct rectal cancer follow-up. Respondents were presented with a scenario in which a rectal cancer patient (TNM stage I–III) had a potentially curative resection. They were asked how often they would use 14 separate surveillance tests during postoperative years 1–5. Repeated measures analysis of variance was used to evaluate if practice patterns were related to the year in which surgeons formal training was completed, controlling for tumor stage and year post surgery. Participants were also asked which tests they would use to further investigate a postoperative raised serum carcinoembryonic antigen (CEA), and a postoperative chest radiograph showing probable metastatic disease. Chi square analysis was used to compare practice patterns to surgeon age.

**Results:** Evaluable responses were received from 347 ASCRS members (19%). Repeated measures analysis of variance revealed no significant relationship between surgeon age and follow-up test ordering schedules. However, follow-up for most modalities was highly correlated with TNM stage and year post surgery, as expected. Practitioner age was a significant factor in the work-up of an elevated postoperative carcinoembryonic antigen test. An unusual relationship was observed in the work-up, with the younger and oldest surgeons ordering more complete blood counts, liver function tests, chest radiographs than the middle two age groups. Younger surgeons employed significantly more colonoscopies than all other age groups combined.

**Conclusions:** Our study shows that post-operative surveillance practices of surgeons caring for patients with rectal cancer do not vary with practitioner age. We propose that continued medical education (CME) has produced this standardized behavior. However, CME has been less successful in homogenizing other areas of respondent's practice, such as in the workup of a raised postoperative CEA. Therefore we conclude that practitioner age accounts for some of the variation in post-operative management of rectal cancer patients.

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#### Macrophages direct microscopic phenotype and clinical outcome in a colon cancer model

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Macrophages (m $\phi$ ) have potent cytotoxic capacity and as such may play a role in controlling metastatic growth by killing tumor cells. By contrast, m $\phi$ , which generally constitute a major component of tumor stroma have recently also been described as promoters of tumor progression by shaping the tumor microenvironment through production of growth and angiogenic factors.

In order to gain more insight in this paradoxical role, we specifically depleted peritoneal m $\phi$  or Kupffer cells (KC; liver m $\phi$ ) of Wag/Rij rats, using liposome-encapsulated dichloromethylene diphosphonate. Subsequently, CC531s syngeneic coloncarcinoma cells were injected intraperitoneally (i.p) or in the portal vein to induce i.p. or liver metastases. Rats were sacrificed on day 9 or 14, and tumors were analysed. Additionally, a survival experiment was performed.

Histopathology of tumors in both peritoneal m $\phi$ -depleted and KC-depleted animals demonstrated a high degree of differentiation (tubulo-papillary growth pattern and well-organized basement membranes) with very little stroma formation (containing no mature m $\phi$ ). In contrast, tumors of control rats showed a desmoplastic stroma reaction with extensive infiltration of m $\phi$  as well as T cells, and hallmark features of malignancy, such as high vascular density, matrix remodelling and poor differentiation, indicating that presence of m $\phi$  is associated with malignant phenotype. Furthermore, mRNA profiles supported more malignant tumor growth as expression of a variety of growth factors, matrix metalloproteinases, and pro-angiogenic factors was upregulated in control tumors. Remarkably however, m $\phi$ -depleted rats bearing highly differentiated tumors displayed larger tumor load that correlated with poorer survival, supporting a crucial role in (initial) anti-tumor responses of m $\phi$  as well.

Thus, even though m $\phi$  play a role in tumor differentiation, directing the tumor into a more malignant phenotype, absence of m $\phi$  results in larger tumor load and shorter survival. This indicates that m $\phi$  exert both tumor killing and tumor promoting capacities. Anti-tumor responses, however, prevail. Selectively antagonizing m $\phi$  functions in malignant progression or enhancing tumor killing capacities might therefore represent important new targets for cancer therapy.

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#### Expression of matrix metalloproteinase-7 and matrix metalloproteinase-9 and its prognostic significance in rectal cancer

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**Background:** The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes involved in tumor invasion; several individual members

of which have been implicated in tumor prognosis. The aim of this study was to evaluate the prognostic significance of MMP-7 and MMP-9 in rectal cancer.

**Methods:** Eighty-seven patients with stage II or III rectal carcinoma who underwent potentially curative resection followed by postoperative adjuvant chemoradiation, and 5-fluorouracil based chemotherapy were investigated immunohistochemically using the monoclonal antibody MMP-7 and MMP-9. Clinical information, including tumor grade, carcinoembryonic antigen (CEA), disease-free survival (DFS), and overall survival (OS) was evaluated and compared with MMP-7 and MMP-9 expression.

**Results:** The median follow-up duration was 53.2 months, and mean patient age was  $55 \pm 11$  years (range 32–75). The expression of MMP-7 correlated significantly with the presence of nodal metastasis ( $P = 0.029$ ). MMP-9 expression was significantly correlated with the depth of tumor invasion ( $P = 0.019$ ). No relationships were found between the MMP-7 and MMP-9 expression and age, sex, tumor size, tumor grade, or CEA level. Univariate analysis showed that MMP-7 expression was associated with poor 5-yr OS (12.8 months vs. 65.3 months,  $P = 0.0405$ ). Multivariate analysis confirmed that MMP-7 was independently associated with adverse outcome (Relative risk: 1.415,  $P = 0.027$ ). However, MMP-9 expression was not related to clinical outcomes.

**Conclusion:** MMP-7 expression was associated with lymph node metastasis and poor 5-year OS in rectal cancer patients.

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#### Abdominoperineal resection or anterior resection for rectal cancer: study of patients' preferences before and after treatment

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**Purpose:** The data in the literature do not allow for the conclusion that the oncological outcomes and the quality of life after anterior resection (AR) are superior to that after abdominoperineal resection (APR). Therefore, patients' preference remains a main reason for performing AR for low rectal cancer. The aim of the study is to evaluate these preferences.

**Methods:** Consecutive patients with rectal cancer (60 prior to surgery, 65 with permanent colostomy and 124 after AR) who visited our out-patient clinic answered the questionnaire on preferences for type of surgery.

**Results:** Preferences for APR, for AR or for leaving decision to a physician were respectively following: prior to surgery group – 5, 30, 65 per cent; permanent colostomy group – 46, 22, 32 per cent and AR group – 4, 68.5, 27.5 per cent. Among patients after surgery who had definite preferences, those after AR more frequently preferred the undergone type of surgery than those with permanent colostomy; 94 vs. 68 per cent, respectively,  $P < 0.001$ .

**Conclusions:** As the small percentage of patients prior to surgery prefers the APR, a shared decision-making process is of value for those with a low rectal cancer. The results suggest that for patients who underwent surgery, sequels after AR are generally perceived as less severe than those after APR. Nevertheless, approximately half of the patients after APR prefers undergone type of surgery, which suggests that perception of a colostomy as a bearable status is higher than it is commonly believed.

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#### Does the surgical scalpel act the role of the second fiddle in the battle against lower two-third rectal cancers? A 5-year follow up study

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**Background:** Gold standard therapy of lower two-third rectal neoplasms is a hotly debated point of the onco-radio-surgical complex treatment, and it is source of boiling discussions.

**Aims:** The authors' aim was to evaluate a 5-y follow-up study regarding to T1–4, N0–2, M0 rectal cancers.

**Patients and method:** Four groups were set up, in each group was 50 patients with lower two-third T1–4 N0–2 stage (there were proved these stages by CT, MRI or rectal USG) rectal cancer. In the first group the patients had been given 50.4 Gy so-called long term three-field irradiation and three or at least two cycles of 5FU base chemotherapy. In the second one the patients had been given 50.4 Gy irradiation, in the third one they had been given a short term ( $4 \times 4$  or  $4 \times 5$  Gy) irradiation before surgical intervention. The fourth one was the control group (following surgical

intervention an adjuvant standard chemo-irradiation). The down staging was strictly examined after neoadjuvant treatments by CT, MRI or rectal USG) There has been examined the overall survival (OS) time to relaps (TR) and disease free survival (DFS). The results were analysed by statistically.

**Results:** Histologically proved total remissions were detected only in the first and second group (4 and 7 patients, respectively). Proportion of clinical response in the three groups were 28%, 18% and 0%, respectively. Proportion of local failure was 12%, 14% and 20%, respectively. The difference between the groups were significant. Histologically proved total remissions were detected only in the long-term irradiated groups, though there is a significant difference depending on whether the patients had been given chemotherapy or not, alongside of the irradiation. There have not been detected local failures at all in the cases of clinical and histological total remissions after surgical interventions. Total remission has not occurred in stage of T4. Only three patients out of 200 were grouped in stage T1.

**Discussion:** The 5-y-survival in cases of total preoperative remission was nearly 100%. It is startlingly few the number of patients with early (T1) disease, and it seems that the proportion of early diagnosis won't change in the future without consistent and well-organised screening systems. In stage of T2 and T3 the neoadjuvant long term irradiation with or without chemotherapy can bring significantly better result than short term irradiation or the adjuvant treatment. In stage of T4 the chance for a successfully radical operation was significantly better after combined long term irradiation with chemotherapy than in the other three groups.

**Conclusion:** The authors recommend on the first place the method of long term three-field neoadjuvant irradiation combined with chemotherapy for T2–4 rectal neoplasms. The authors have proved the advantage of neoadjuvant treatment for rectal cancer instead of primarily used surgical intervention. It is possible that the surgical scalpel is inevitable part of the treatment these days but its main role must be shared with other pretenders.

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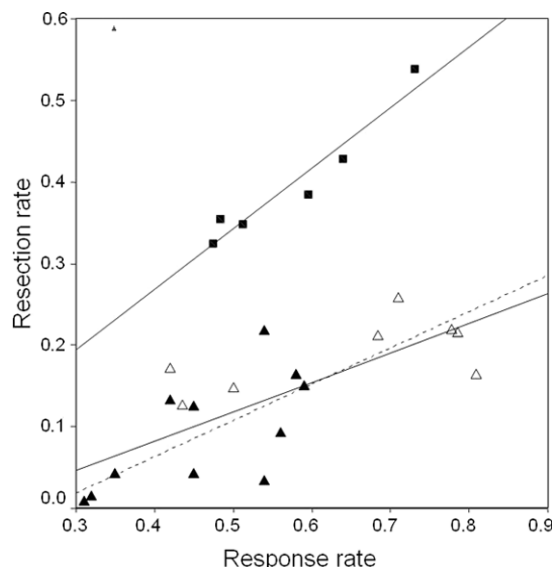
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#### Correlation of the rate of liver resection to the rate of tumor response in patients with metastatic colorectal cancer

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**Introduction:** Long-term survival is reported in patients with liver metastases of colorectal cancer. Recently, an increased number of reports on liver resection following neoadjuvant chemotherapy in patients with initially unresectable liver metastases has been published.

**Methods:** We analyzed all published or presented trials and retrospective studies that report the rate of objective response and the rate of resection of initially unresectable metastases to correlate of objective response and the rate of resection of metastases.



**Results:** In studies that enrolled patients with metastases confined to the liver, 24 to 54% of patients were resected following chemotherapy, compared to 1 to 26% of patients in trials that included non-selected patients with metastatic colorectal cancer. A strong correlation was found between response rates and the resection rate in studies with patients with