(TIL p: 0.0087) none of the other examined factors affected local recurrence rate in the present series: nodal status (NS p: 0.83), lateral spreading (LS.p: 0.76), lymphatic vessel invasion (LVI p: 0.347), blood vessel invasion (BVI p: 0.197), perineural invasion (PI p: 0.22). On the other hand overall survival is correlated with most of the above mentioned parameters and is inversely matched with the presence of lymphocyte infiltrate (TIL p:0.0001, NS p:0.0028, LS p:0.0067, LVI p: 0.058, BVI p: 0.352, PI p: 0.0003).
**Conclusions:** The present data are indicating the lymphocyte infiltration as a major prognostic factor in predicting the risk of local or distant relapse in rectal cancer patients.

**679** PUBLICATION

**Oncological results of hepatectomy associated with radiofrequency ablation of strictly unresectable liver metastases T in 63 patients with colorectal primary**

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**Background:** Results and indications of intra-operative radiofrequency (RF) ablation of liver metastases (LM) are not well defined in the literature.
**Aim:** To appreciate the survival rate of patients with strictly unresectable LM (defined on technical but not oncological criteria) when undergoing liver resection plus RF, along with recent systemic chemotherapy.
**Patients and methods:** Sixty three patients with technically unresectable LM (either >5, or bilateral with no sparing at least one sector of the liver, or with tumor proximity to central major vascular structures) were treated by segmental anatomic resection (44 patients, 142 LM) when LM were large, with wedge resection (36 patients, 55 LM) when LM were peripheral and small, and with RF (63 patients, 154 LM) when LM were central and small. Extrahepatic metastases were also resected in 27%. All patients received perioperative chemotherapy. The median follow-up was 27.6 months (range: 15–74).
**Results:** There was no postoperative mortality and the morbidity rate was 27%. The 2-year overall survival rate of the 63 patients was 67% with a median survival of 36 months. In comparison, the median survival of similar patients treated classically with systemic chemotherapy alone is (was?)18 months. The local recurrence rates were similar for the 3 types of local treatments: 7.1% for the 154 RF ablations, 7.2% for the 55 wedge resections, and 9% for the 44 segmental anatomic resections (p = 0.216). Hepatic recurrences occurred in 71% of patients.
**Conclusion:** The combination of anatomic segmental resection, wedge resection, RF ablation, and recent systemic chemotherapy in patients with really unresectable LM results in a median survival of 36 months, and appears as a real improvement in survival.

**680** PUBLICATION

**Chemoradiation with raltitrexed in preoperative treatment of stage II/III resectable rectal cancer: long term results of a phase II study**

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**Background:** Aim of this study is to evaluate the impact of a neodjuvant chemoradiation with raltitrexed on tumor response and long term results, in patients with locally advanced resectable rectal carcinoma.
**Material and methods:** Between 1998 and 2002, 39 patients were treated with preoperative chemoradiation, IV bolus of raltitrexed on days 1, 19 and 38 and concurrent 50.4 Gy (1.8 Gy/day) external beam radiotherapy. Surgery was performed 6–8 weeks after the end of chemoradiation. A 10 Gy IORT boost was delivered to the tumor bed. Patients with positive nodes at pathological examination underwent adjuvant with 5-FU-leucovorin (Machover regimen).
**Results:** All patients had T3 tumor at diagnosis, the N stage was: cN0 9 patients, cN1 19 patients and cN2 11 patients. All patients underwent surgery. The median follow-up was 58 months (range 34–79). Of 39 patients 24 (61%) downstaged at T level and 27 (69%) at N level. The pT stage was pT0 9 patients (23%), pTmic 7 patients (18%), pT1 2 patients (5%), pT2 6 patients (16%), pT3 13 patients (33%), and pT4 2 patients (5%). According to TRG (Tumor Regression Grade)classification patients were: TRG1 23% (9/39), TRG2 18% (7/39), TRG3 38% (15/39), and TRG4 21% (8/39). Five years OS was 91.7%, LC was 97.4% and MFS was 72.2%. Patients were grouped according pT (T0–2 vs T3–4), TRG (TRG1–2 vs TRG3–4), c N (cN1–2 vs cN2) and p N stage (pN0 and pN+). The cN stage wasn't statistically correlated with 5-year outcomes: OS was equal in the two group of patients; LC was 100% and 90.0% in cN0–1 and cN2, respectively; MFS was 78.5% in cN0–1 and 54.5% in cN2. Of postoperative parameters pT didn't show correlation with OS, a difference, even if not significant, was found for LC (100% in pT0–2 vs 93% in pT3–4) and MFS (82% in pT0–2 vs 58.7% in pT3–4); TRG showed a not statistical correlation with LC (100% in TRG1–2 vs 95.5% in TRG 3–4) and MFS (93.7% in TRG1–2 vs 61% in TRG 3–4), OS was equal in the 2 group of patients; pN was the strongest post-treatment factor in influencing the outcomes at 5 years: OS was 91.7% and 77% in pN0 and pN+ patients respectively (p = ns), LC was 97.4% and 90% in pN0 and pN+ patients respectively (p = ns), MFS was 72.2% and 52.6% in pN0 and pN+ patients respectively (p = 0.025).
**Conclusion:** Preoperative chemoradiation with raltitrexed showed and high rate of tumor downstaging, with an elevated percentage of pathological major response (pT0-mic 41%). Results were excellent in terms of OS and LC. The 5-years MFS was 72.2% and was statilstically correlated pN status. A longer follow-up is needed to confirm data. Validation of pretreatment prognostic factors will help to select patients to treat with more aggressive chemoradiotherapy combination.

**681** PUBLICATION

**Phase I study of concurrent chemoradiation including twice-weekly low dose gemcitabine for unresectable pancreatic adenocarcinoma**

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**Purpose:** To determine the maximum tolerated dose (MTD) and dose-limiting toxicities, as well as potential antitumor activity of twice-weekly gemcitabine and concurrent irradiation in patients presenting with unresectable locally advanced, or metastatic and painful pancreatic adenocarcinoma.
**Patients and methods:** Thirty patients with histologically proven adenocarcinoma of the pancreas have been treated in Centre Hospitalier Lyon Sud, France, between 2000 and 2005. The initial dose of gemcitabine was 30 mg/m$^2$ by 30-minute intravenous infusion twice a week, for 5 consecutive weeks concurrent with 50 Gy of radiation within 5 weeks, delivered to the pancreatic area. Gemcitabine doses were escalated in 10 mg/m$^2$ increments in successive cohorts of three to six patients until dose-limiting toxicities were observed. A limiting toxicity is defined as a grade 4 or 5 toxicity.
**Results:** Thirty patients have been included, mean age 57 years old (41–73), 20 male and 10 female, 30 are evaluable for toxicity. Concurrent radiation and twice-weekly gemcitabine at 30-, 40-, 50-, 60-, 70 mg/m$^2$ were well tolerated, without limiting toxicities observed. All patients received the full dose of radiation, and 16/24 (67%) patients received at least 70% of the prescribed dose. This study currently explores the level 80 mg/m$^2$ twice a week.
**Conclusions:** This work is still in progress, until the MTD is reached. The complete cohort of patients will be finally analyzed for toxicity and for survival and relapse patterns, and will be followed by a phase II study to ascertain the feasibility of this scheme, with the recommended dose of twice-weekly gemcitabine, when evaluated. The next phase I trial will include oxaliplatin in addition to gemcitabine and radiation, for the same type of patients. Complete results will be presented during the meeting.

**682** PUBLICATION

**Laminin-5-gamma2-chain during the colorectal adenoma-carcinoma-sequence: from primary anchoring protein to an invasion promotor**

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**Background:** The glycoprotein Laminin-5 is a key protein of the epithelial cell adhesion complex, providing cell anchoring to the basement membrane in normal colorectal mucosa. The γ2 chain of Laminin-5 (Ln-5 γ2) plays a pivotal role in cell migration and, possibly, as an invasion promotor in colorectal carcinomas. This study was performed to test whether there are and if yes, which changes occur in immunohistochemically detected Ln-5 γ2 pattern during the malignant transformation of colorectal adenomas.
**Material and Methods:** Paraffin specimens of full rectal wall specimens of low (n = 55) and high grade (n = 13) neoplastic colorectal adenomas, colorectal carcinomas (n = 37) and normal colon (n = 60) were assessed histopathologically and immunohistochemically for Ln-5 γ2 changes using the monoclonal antibody D4B5.
**Results:** A significant increase of immunohistochemically detected Ln-5 γ2-alterations associated with migration and invasion were described, i.e. loss of Ln-5 γ2 to the basement membrane, stromal deposition and intracellular increase of Ln-5 γ2 from low grade neoplastic adenoma to

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 γ2 – positive small blood vessels were detected in the invasion zone of 35% of all carcinomas, indicating a role for Ln-5 γ2 in tumour angiogenesis.
**Conclusion:** Our data show a distinct change of Ln-5 γ2 immunohistochemical pattern during colorectal adenoma-carcinoma-progression; adenomas with higher risk of malignant transformation or increased invasive potency can be identified by Ln-5 γ2 immunohistochemistry.

**683** PUBLICATION

**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 respectable 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$^2$) and oxaliplatin (130 mg/m$^2$) 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; $pT_{mic}$N0M0, 6 patients; $pT_{mic}$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 $pT_{mic}$), 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.

**684** PUBLICATION

**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.

**685** PUBLICATION

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

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Macrophages (mφ) have potent cytotoxic capacity and as such may play a role in controlling metastatic growth by killing tumor cells. By contrast, mφ, 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 mφ or Kupffer cells (KC; liver mφ) 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 mφ-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 mφ). In contrast, tumors of control rats showed a desmoplastic stroma reaction with extensive infiltration of mφ as well as T cells, and hallmark features of malignancy, such as high vascular density, matrix remodelling and poor differentiation, indicating that presence of mφ 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, mφ-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 mφ as well.
Thus, even though mφ play a role in tumor differentiation, directing the tumor into a more malignant phenotype, absence of mφ results in larger tumor load and shorter survival. This indicates that mφ exert both tumor killing and tumor promoting capacities. Anti-tumor responses, however, prevail. Selectively antagonizing mφ functions in malignant progression or enhancing tumor killing capacities might therefore represent important new targets for cancer therapy.

**686** PUBLICATION

**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