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Postoperative adjuvant chemotherapy with or without radiotherapy for rectal cancer

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Background: To determine whether the addition of radiotherapy to postoperative adjuvant chemotherapy results in improved disease-free survival and overall survival in AJCC stage II and III rectal cancer

Materials and Methods: From 1989 to1999 144 patients with AJCC stage II and III rectal cancer treated with radical surgery and postoperative CT or CCRT were included in a prospective non-randomized study. Of 144 patients, 72 patients were treated with postoperative CT alone and the other 72 patients with postoperative CCRT. The chemotherapy regimen mainly consisted of oral UFT on a daily basis for 1-12 months (median 12 months) or 5-FU (500mg/m^2 for 5 days) intravenous (IV) chemotherapy with 4 week intervals for 1-18 cycles (median 6 cycles) and leucovorin. Radiotherapy with 4500 cGy was delivered to the surgical bed and regional pelvic lymph nodes area followed by 540-1440 cGy (median 540 cGy) boost to the surgical bed. The follow-up period ranged from 20 to 150 months with a median of 44 months.

Results: The 5-year overall survival (OS) was 60.9% and 68.9% (p=0.0915), and the 5-year disease-free survival (DFS) was 56.1% and 63.8% (p=0.3510) for postoperative CT and postoperative CCRT, respectively. For stage II, the 5-year OS was 71.1% and 92.2%, and the 5-year DFS was 57.3% and 85.4% for postoperative CT and CCRT, respectively. The OS was significantly improved (p=0.0379) and the DFS was slightly improved but didn't show any statistical difference (p=0.1482) for postoperative CCRT compared to postoperative CT alone for stage II. In the patients with stage III, the 5-year OS was 52.0% and 55.0%, and the 5-year DFS was 47.8% and 49.8% for postoperative CT and postoperative CCRT, respectively. There were no statistically significant differences between postoperative CT and CCRT (p=0.4280 and p=0.7891) in OS and DFS for stage III.

Conclusions: This study showed that postoperative CCRT compared with CT alone significantly improved OS in stage II without lymph node metastasis but not in more advanced stage III with lymph node metastasis.

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Continuous infusion of oxaliplatin plus chronomodulated capecitabine in advanced colorectal cancer (CRC): a feasibility study

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Background: the combination of oxaliplatin and capecitabine or XELOX, is an effective and safe approach to the treatment of advanced CRC. Aim of the study was to define the feasibility and toxicity of XELOX administered through a new and original schedule in different lines of chemotherapy. Response rate was evaluated. Chronomodulated capecitabine could be a convenient oral alternative to chronomodulated infusional 5-FU combined with infusional oxaliplatin to further improve therapy in this setting.

Material and methods: between May 2002 and January 2003 26 CRC patients entered the study. Patients characteristics: male/female: 16/11; performance status according to ECOG: 0 (15), 1 (9) and 2 (2); median age: 65 (32-77); 61.5% (16/26) >1 metastatic site; 30.7% (8/26) > 2 metastatic sites; sites of metastases: liver (14), lung (11), peritoneal involvement (4), local (5), nodes (12). Treatment: oxaliplatin 70 mg/mq c.i. for 12 hrs (8.00 a.m. to 8.00 p.m.) d 1,8 plus chronomodulated capecitabine 2000 mg/mq/die os (h 8.00 a.m. 25% of total dose; h 6.00 p.m. 25% of total dose; h 11.00 p.m. 50% of total dose), d 1-14. Every 21 days. 93 cycles infused.

Results: toxicity G3/4: 26 patients evaluable. Most frequent related G3/4 adverse reactions were diarrhoea 8/26, nausea/vomiting 1/26, neuropathy 1/26, asthenia 2/26, hand-foot syndrome 1/26, neutropenia 1/26, transaminitis 1/26. G3/4 anemia and leucopenia have not been observed. Moreover, no G3/4 mucositis has been recorded. No pts withdrew due to adverse events. Response rates: 1° line (10 patients, 9 evaluable for clinical response): 5 PR (55.5%), 1 CR (11%), 3 P (33.5%). Patients treated in following lines (16 patients, 9 evaluable at moment): 3 PR (33.5%), 3 SD (33.5%), 3 P (33.5%). Moreover, we observed 2 PR, 3 SD and 2 P in patients previously progressed with oxaliplatin-based regimens.

Conclusions: this schedule appeared to be highly active and feasible with low incidence of G3-4 toxicities. This study is ongoing until 46 evaluable patients will be enrolled.

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Preoperative chemoradiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer

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Background: Local recurrence was noted in more than 20% of patients (pts) with a circumferential resection margin (CRM) of 1 mm or less. However, securing an adequately long CRM can be difficult in some pts. We have used preoperative chemoradiotherapy in combination with intraoperative electron beam radiation (IORT). We irradiated the electron beam over the entire surface of the resected pelvic wall to create a new tumor-free margin because the absorbed dose of IORT is densely distributed in the shallow area from the irradiated surface. The outcome of pts treated with this approach was retrospectively compared with the pts treated with surgery alone.

Methods: Between 1991 and 2001, 98 pts of adenocarcinoma of the middle or lower-third of the rectum and a preoperative diagnosis of cT3-4NxM0 underwent surgery following the preoperative irradiation(XRT) of 20 Gy in 10 frs. [RT group]. 67 pts between 1991 and 1998 received only preoperative XRT [preRT group], while 32 pts in 1999 and thereafter were given oral Tegafur/Uracil (UFT) concurrently [preCRT group]. Radical surgery was performed approximately 2 weeks after the completion of XRT. 82 pts with resectable adenocarcinoma of the rectum (pT2-4NxM0) treated by surgery alone during the same period were compared as the control. [NoRT group]

Results: No significant difference was observed in pts characteristics and morbidity rate between the RT and the NoRT groups. Local recurrence was observed in 2 pts (2%) in the RT group and in 11 pts (13%) in the NoRT group; the rate in the RT group was significantly lower than that in the NoRT group (p = 0.004). Distant metastasis was seen in approximately 20% in each group. The disease-free survival (DFS) in the RT group was significantly better than that in the NoRT group (p = 0.04). The 5-year DFS was 71% and 59% in the RT group and NoRT group, respectively. The over-all survival (OS) in the RT group was significantly better than that in the NoRT group (p = 0.03). The 5-year OS was 82% and 65% in the RT group and the NoRT group, respectively. A subgroup analysis did not exhibit obvious downstaging in the preCRT group. However, the percent of tumor shrinkage was 22 ± 11% in the preRT group and 35 ± 11% in the preCRT group, with a significantly higher value in the preCRT group (p < 0.001). Sphincter preservation (SP) was possible in 78% of the pts. in the preCRT group, and this was significantly higher than that in the preRT group (41%; p = 0.002).

Conclusions: Combined preoperative and intraoperative radiation therapy against cT3-4Nx rectal cancer significantly reduces the local recurrence and significantly improves prognosis. Preoperative chemoradiotherapy using oral UFT increases SP without increasing adverse reactions.

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Down-regulated expression of thymidyalte synthase protein and messenger rna by oxaliplatin in colon cancer cells

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In the past years, we designed an innovative HDFL24 regimen using high-dose weekly 24-hour infusion of 5-FU (2,600 mg/m^2) and leucovorin (300 mg/m^2) in the treatment of CRC. The overall response rate was 42.9% with surprisingly low myelotoxicity and other treatment-related toxicity (J Clin Oncol 1994;12:875; Anticancer Res 1997;17:3867). For further improve the treatment response, combining HDFL with new effective anti-cancer agents (such as oxaliplatin, irinotecan) are used. In the first-line treatment for metastatic CRC, either Oxaliplatin-HDFL or Irinotecan-HDFL may achieve a response rate of more than 50%. However, in the salvage treatment for metastatic CRC patients who had failed or progressed after 5-FU/LV (especially HDFL), only *Oxaliplatin-HDFL* may achieve a salvage response rate of about 13-25%. Irinotecan-HDFL or oxaliplatin alone had very poor salvage response (response rate of about 5% or less). We hypothesize that oxaliplatin may reverse the HDFL-related drug resistance via pivotal unknown mechanism(s).