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The role of intraoperative radiotherapy in the adjuvant treatment of stage II, III rectal carcinomas

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Purpose: To reduce late gastrointestinal toxicity and increase local control a pilot study was initiated, in which patients received a moderate dose external beam irradiation (41.4 Gy) plus chemotherapy prior or after surgery and, in addition, an electron beam boost (10 Gy).

Patients and Methods: Until 12/94 104 patients with clinically advanced cT3, T4 or N+ carcinomas had IORT. Efficacy was analysed in 63 patients with a stage II and III rectal carcinoma after pathohistological examination of the specimen, including 9 patients with R1-resection. (radiochemotherapy (IO-EBRCT) n = 45, radiotherapy IO-EBRT) n = 18). The median follow-up was 30.6 months.

Results: Local tumor control was markedly improved. 2 patients revealed an infield failure 18.3 and 21.9 months after IO-EBRCT (tumor control 95.5%). A 100% local tumor control could be achieved in pat. after IO-EBRT. The 4-year actuarial overall and relapse-free survival was 97% and 82% in pat. after IO-EBRCT and 81% and 59% in pat. after IOEBRT. The distant metastases rate was reduced by adding chemotherapy (17.6% vs. 34%). No late toxicity was observed.

Conclusion: With moderate dose IO-EBRT high local tumor control rates and improved survival data could be obtained while late therapy related morbidity was reduced.

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Radiotherapy alone in curative sphincter preserving management of rectal cancers

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Curative radiotherapy alone for rectal adenocarcinomas was delivered to 151 patients (pts) with a curative intent. Pts were clinically staged according to size (T1 < 3 cm, T2 > 3 cm) and depth of infiltration: A = superficial, B = impaired mobility and T3 fixed. Over the past 6 years, transrectal ultrasound was used systematically. Intracavitary contact X-rays (ICXR) was used alone in 69% or combined with interstitial brachytherapy in 7.5%. External radiotherapy (XRT) with either contact or brachytherapy was given to 23.5% of the pts Local control rate with sphincter preservation was achieved in 63%. A local failure (LF) was observed in 50 cases (28%). 39 LF were amenable to salvage surgery. After salvage treatment, the ultimate failure rate is 18.3%: 14 pts with pelvic failure (10.3%) and 10 pts (8%) with local and metastatic failures. The ultimate local control was 82%. Actuarial survival is 57% at 5 years. There is no difference in local control or survival according to the differenciation (p = 0.69), UICC staging system (p = 0.47), size (p = 0.43) or distance to anal margin (p = 0.72). Grade 3 late effects are of 3.8%. The sphincter function after irradiation was normal in 118/124 pts (95%). ICXR is the treatment of choice for T1A. XRT is indicated in the treatment of tumors with impaired mobility (T2B). Clinical staging and transrectal ultrasound allows a safe selection of indications. Radiotherapy alone may be proposed in selected cases as an alternative to mutilating surgery for rectal adenocarcinomas.

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Randomized phase III trial of active specific immunotherapy (ASI) versus control in patients with Duke's B2, B3 or C colon cancer

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Purpose: This randomized phase III study tried to evaluate the influence of ASI as an adjuvant in patients (pts) with stages B2, B3 and C colon cancer. Contrary to the reference study (Hoover et al, J Clin Oncol 11: 390, 1993) pts in the ASI arm received 4 rather than 3 vaccinations (30, 37, 44 and 180 days intradermally, postsurgery).

Methods: Autologous tumor cell (ATC) vaccines were prepared as described previously by Peters et al (Cancer Res 39: 1353, 1979). The first 2 vaccines contained 10^7 irradiated ATCs and 10^7 BCG (Tice) organisms. The last 2 vaccines contained only irradiated ATCs. Pts were stratified for institution, disease site and Dukes' stage. Both arms of the study were balanced for gender, age and the number of positive lymph nodes in those with Dukes' C.

Results: Median follow-up is 4 years and 4 months. Toxicity included mainly local ulceration (98%), enlarged regional lymph nodes (67%) and fever and/or chills (<24 h; 40%)

	ALL patients (n = 254)		Stage B patients (n = 170)	
	CTR	ASI	CTR	ASI
Recurrences	28%	16%	23%	9%
Deaths	25%	17%	25%	13%

Conclusions: ASI induced a proportional reduction in recurrence of 43%, in deaths of 32%. Standard application of ASI in Dukes B2, B3 colon cancer pts should be considered.

723 POSTER

Pneumoperitoneum and port-site metastases in laparoscopy for cancer

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Laparoscopic resection for cancer is controversial and port-site metastases are not infrequent. The mechanisms of occurrence of port-site metastases remain unclear. Animal experiments have suggested a role for carbon dioxide (CO_2). On the other hand, port-site metastases also occur after thoracoscopy, where no CO_2 is used. Aim of this study was to define the role of CO_2 in seeding of tumor cells in the human patient.

Staging laparoscopies for pancreatic cancer were used as a model, because of the presence of a mutation on the k-ras gene, allowing the detection of low levels of tumour cells. After PCR, presence of mutations in the codons 12 and 13 of k-ras gene was determined by restriction fragment length polymorphisms.

Morphologically, the pathologist suspected tumor cells in 6/12 peritoneal samples, 4/11 instruments, 4/12 trocars and 2/7 suction devices, but in none/12 CO_2 samples. After gene amplification, low levels of tumour cells were detected by PCR in 4 out of 12 aerosols. Six aerosols did not contain any DNA, as confirmed by a second PCR. Two aerosols were borderline.

During staging laparoscopy for pancreatic cancer in humans, even in the presence of massive peritoneal contamination, the risk of seeding of tumour cells by CO_2 is markedly lower ($1:10^4$, Kruskal-Wallis, df = 11, $p < 0.0001$) than the risk of mechanical inoculation by the instruments. These results suggest that – in most cases – port-site metastases might be preventable, if mechanical contamination of the port-sites can be avoided.

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Phase I study of radioimmunoguided surgery (RIGS) with anti-CEA single chain Fv antibody in colorectal cancer

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The aim of this study is to investigate the potential of RIGS® with an anti-CEA single chain Fv (scFv) antibody derived from bacteriophage technology (Chester et al, 1994) to detect residual small volume disease in patients with primary and recurrent colorectal cancer. The RIGS system is based on the preoperative injection of a radiolabelled antitumour antibody and the intraoperative detection of radioactivity by a hand-held gamma-detecting probe (Neoprobe® 1000 instrument). ScFv antibodies consist of the variable heavy and the variable light chain region joined by a flexible linker.

Patients receive 1 mg MFE-23-his labelled with ^{125}I to a specific activity of 185 MBq/mg 24, 48 or 72 hours prior to operation. Results of the probe are correlated with histology and counting the excised specimen in a laboratory gamma counter.

Preliminary results with both methods and histology show selective tumour localisation in patients undergoing resection of liver metastases at 72 hours after administration of the antibody. Rapid excretion of the radiolabelled scFv was shown by a tumour to blood ratio of 13:1. In 3 patients undergoing resection of their primary tumour at 24 hours the RIGS method showed a positive finding, but was not confirmed by laboratory gamma counting.

These results show the successful preparation and use of scFv antibodies for RIGS procedures Antibody localisation is superior at 72 hours than at the earlier time point.