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Phase II study of docetaxel (D) as salvage chemotherapy in patients with advanced gastric cancer

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Introduction: D has considerable antitumor activity as first line chemotherapy in gastric cancer. The present study investigated D as second line treatment in metastatic disease. D was given at a dose of 100 mg/m^2 i.v. every 3 weeks.

Patients and Methods: 27 pts. with documented disease progression while receiving 5-FU containing regimens (17 pts. with 5-FU/Cisplatin) were entered onto the study. Median age 57 years (46–66), M/F ratio 20/2, WHO PS 1 (0–2).

Results: 25 pts. with a total of 98 cycles are evaluable for response and safety. Short lasting Neutropenia of NCI-CTC grade 4 occurred in 60% of pts. No other toxicities of NCI-CTC grade 4 have been observed. The incidence of non-hematological toxicities of NCI-CTC grade 3 was 8% for neuropathy and asthenia, 4% for mucositis and diarrhea respectively. No treatment related death occurred.

Response: One CR and 4 RP corresponding with an overall response rate of 20% (95% CI: 7–41%) were achieved. Stabilization of disease have been observed in 8 (32%) of response evaluable patients, resulting in a tumor growth control rate of 52% (95% CI: 31–72). 4 PR have been observed in a subgroup of 17 pts. after prior exposure to HD Fol/5-FU and Cisplatin.

Conclusion: Docetaxel is active as second line CT in metastatic gastric cancer after prior exposure to 5-FU and Cisplatin based regimens

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Transhiatal oesophagectomy in the treatment of carcinoma of the lower oesophagus and cardia of the stomach – Influence of preoperative risk factors

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Background/Aims: Despite all advances in surgical treatment and efforts in the postoperative management of patients with carcinoma of the lower oesophagus and cardia, morbidity, mortality and late results are disappointing. A comparative randomised study evaluate preoperative risk factors in three groups.

Materials and Methods: One-hundred and twenty-five patients with adenocarcinoma of the lower oesophagus and the cardia of the stomach referred to Surgical Clinic between 1990 and 1996. In fifty patients the disease was staged $T_2N_1M_0$ with the tumour supposedly restricted to oesophageal or gastric wall. Based on the "scoring system" reported by Siewert all patients who subsequently underwent transhiatal oesophagectomy had detailed preoperative assessment and were divided in three groups of risk.

Risk	Score Points	N	Complications	Mortality
Low Risk	12–15	12	8	1
Moderate Risk	16–21	22	8	3
High Risk	22–37	16	12	6
Total	–	50	28	10 (20%)

Conclusions: Siewert's scoring system is reliable and highly predictive for morbidity and mortality after transhiatal oesophagectomy in cancer patients.

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3-Dimensional planned conformal radiation technique (3D-RT) compared to standard 2 isocentric fields AP-PA radiation technique (APPA-RT) in anal cancer

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Purpose: Escalation of radiation dose intensity (RDI-total dose per overall treatment time) in chemoradiation for anal cancer seems to be necessary to improve locoregional control, but APPA-RT then results in more severe toxicity. 3D-RT, which spares radiation sensitive regions of vulva and ventral parts of the bladder, may allow to raise RDI without increasing toxicity or relapse risk.

Methode: 23 anal cancer patients were treated with chemoradiation 12/96–2/99. All patients had prior to radiation a computertomography for 3-dimensional planning. The dose-volume histogramms (DVH) of vulva, bladder, planning target volume (PTV-derived from a Co60 radiation technique used 1990–1996) and two high dose volumes (HDV-body volume confined by the 80% (HDV-80%) and 100% (HDV-100%) isodoses) of APPA-RT and 3D-RT were compared. 3D-RD consists of 4 isocentric MLC-shaped fields with gantry angle 40°–45°, 90°, 270° and 315°–320°.

Results: A significant reduction of Dmedian to vulva ($p < 0.001$) and bladder ($p < 0.001$), Dmax to PTV ($p < 0.001$) and of volume of the HDV-80% ($p < 0.001$) and HDV-100% ($p < 0.001$), but a significant increase of Dmin to PTV by the 3D-RT in comparison to APPA-RT.

Conclusion: 3D-RT may reduce the risk of acute toxicity in anal cancer patients and allow to increase RDI without severe toxicity. The dose distribution in PTV is more homogenouse in 3D-RT than in APPA-RT. Clinical datas of chemoradiation with 3D-RT will be provided.

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Whole body hyperthermia (WHB, 41.8°C) in combination with chemotherapy in gastrointestinal (GI) cancer

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Purpose: Platinum derivatives are promising substrates in the treatment of GI-tumors. Since hyperthermia is known to enhance their therapeutic index, the aim of the present study was to investigate toxicity and efficacy of WBH (41.8°C) in combination with carboplatin (CBDCA) and 5-fluorouracil (5-FU)/leucovorin in patients with advanced pancreatic or biliary tract cancer.

Methods: 14 pts. with pancreatic (7) or biliary tract (7) cancer, median age 60 (37–64) and performance status (WHO) 0–2 are so far included. WBH was administered by a radiant heat device (Enthermics Medical Systems). CBDCA (AUC 4.5, 30 min i.v. infusion) was administered after reaching the core temperature of 41.8°C, which was maintained for 60 min. Thermochemotherapy was preceeded or followed by 5 days of 5-FU 425 mg/m^2 and leucovorin 20 mg/m^2. This regimen was repeated every 28 days. Tumor assessment was done following cycle 2 and 4.

Results: 40 cycles were evaluable. No objective responses were seen in pts. with pancreatic cancer (3 SD, 4 PD after 2 cycles). In pts. with biliary tract cancer there were 2 partial responses, disease stabilisation in 4 pts. with clinical improvement in 2 and one death due to septic complications. Toxicities (WHO 3–4) included: neutropenia (1 cycle); thrombocytopenia (6); anemia (4); mucositis (2); diarrhea (4). Due to severe thrombocytopenia or leukopenia treatment had to be delayed in 6 cycles. Delays were only seen, when 5-FU/leucovorin preceeded CBDCA.

Conclusion: No unexpected toxicities were seen with concurrent systemic hyperthermia. Thermochemotherapy is active in biliary tract carcinoma and is warranted for further evaluation. As a result of this study we initiated a trial to investigate the effect of WBH in combination with oxaliplatin in pt. with colorectal cancer.

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The role of different preoperative treatment modality in esophageal carcinoma management

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Purpose: The routine use of adjuvant radiotherapy as a single modality is presently not warranted on the basis of majority randomized trials Investigation of influence of additional use of intracavitary brachytherapy (IBT), hyperthermia (HT) and hyperglycaemia (HG)

Methods: 243 untreated cases of esophageal squamous cell carcinoma were entered in the study. 54 patients were treated with surgery alone, the rest 189 received external beam radiotherapy (RT) to a total dose 30 Gy/6 fractions/8 days in preoperative period. The 57 patients of 2nd group received in preoperative period external RT only. IBT was administered to 59 patients in 2–3 days after RT (the 3rd group). The average dose delivered by IBT (^{137}Cs, LDR-MDR or ^{60}Co, HDR-MDR) was 15 Gy/3 fractions. Thermoradiotherapy was used for 37 patients in the 4th group. Intracavitary SHF-HT sessions (t ≈ 42.5–44°C) were provided in 2 hours after RT each

72 hours; the duration of HT-session was 45–50 min. In the 5th group (36 patients) we used HG 30–50 mmoll/l during 90–100 min. combined with HT after RT. Surgery was earned out after 14–16 day rest in all groups except 1st.

Results: Simultaneous application of RT, HT and HG intensified tumour damage, but increased the level of postoperative complications. The resection rate of the S, RT, RT + IBT, RT + HT and RT + HT + HG groups was 33.3%; 58.8%; 78.7%; 70.0% and 85.7%. The 3-year survival rates of the resected groups were 19.1%; 24.6%; 34.1%; 29.7% and 27.8%; accordingly.

Conclusion: The additional application of intracavitary irradiation is the most effective and safe proposed regimens.

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Concurrent chemoradiotherapy using low-dose continuous infusion of 5-fluorouracil for stage 2–3 esophageal cancer: A 3-year follow-up report

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Purpose: To improve local control of locally-advanced esophageal cancer, concurrent chemoradiotherapy with 5-fluorouracil (5-FU) infusion was tried under the cooperation of the Niigata RCT Research Group.

Material and Methods: 31 patients with stage 2–3 esophageal cancer were treated with the concurrent chemoradiotherapy using continuous infusion of 5-FU (250~300 mg/m^2 per 24 hours) for 5 days per week given over 25 to 35 days (RT + FU group). Treatment results were compared with the historical control of 27 patients treated with radiotherapy alone (RT group).

Results: The chemoradiotherapy regimen was well tolerated. Response rate (CR + PR) of 94% in the RT + FU group was significantly higher than 63% in the RT group ($p = 0.01$). Median local progression-free time of 31.2 months in the RT + FU group was significantly higher than 4.0 months in the RT group ($p = 0.02$).

Conclusion: This chemoradiotherapy regimen is significantly superior to conventional radiotherapy alone in locoregional control of stage 2–3 esophageal cancer.

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Intra-arterial chemotherapy (iaCT) combined with radiation (RT) for advanced pancreatic cancer

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Purpose: To evaluate the efficacy of intra-arterial infusion of cytostatic drugs combined with radiation in the treatment of patients with locally advanced and metastatic pancreatic cancer.

Methods: 29 patients were included in the trial. Catheters were inserted angiographically into celiac axis (18 pts.) or a.lienalis (11 pts.) and left in place for 4 consecutive days for each cycle. 5-FU (2–2.5 g/m^2), ADR (50–60 mg/m^2) and cis-DDP (40–50 mg/m^2) were infused over 120 min for 4 consecutive days. Radiation was started 3 days later and given in 5 daily fractions (2.5 Gy) per week (total dose 30 Gy). Combined treatment was given in a median of three cycles.

Results: Ten (34%) partial response was observed, as were thirteen cases (45%) of stable disease and six (21%) of progressive disease. Median disease free survival was 11.3 months. Toxicity was generally mild to moderate; leucopenia (8/29), nausea and vomiting (12/29) predominated.

Conclusion: iaCT with RT is feasible and well tolerated. This combination results in the improvement of local control in patients with advanced pancreatic cancer.

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Combination therapy with Oxaliplatin + Gemcitabine in advanced pancreatic cancer

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Encouraged by treatment results with a combination of oxaliplatin + 5-FU/FA in 10 patients suffering from colorectal and gastric cancer with 3/10 PR, 1 MR and 4 SD (8/10 second line, 8/10 tumor recurrences) we now treated in a pilot study 9 patients (2 m, 7 f, age 38–76) with advanced pancreatic cancer (n = 3 locally advanced recurrence (LR), n = 3 T3N1 tumors, 1 of these 3 tumors with ascites, and n = 2 with LRM1 and T3N1M1 tumors resp.), without prior chemotherapy, with a combination of Gemcitabine (G) + Oxaliplatin (Ox) by systemic i.v. application: G (mean 700 mg/m", 30 min. infusion) + Ox (mean 70 mg/m", 4 h infusion) on day 1 and 700 mg/m" Gemcitabine (30 min. infusion) on day 8, followed by a new cycle every 2 weeks. Treatment duration: 5, 5, 5, 6, 6, 6, 7, 8, >10 months. In case of allergic reactions, severe neuropathy or tumor progression therapy was partly continued by Gemzar-monotherapy or 5-FU/FA or Campto and Caelix resp. Diagnosis was confirmed by clinical signs, imaging methods, operation and/or histology. Efficacy was evaluated by clinical signs, US, CT, in special cases by MR and PET, and tumor markers, mostly CA 19-9 (determined every 4 weeks). Treatment resulted in 4 PR, 2 MR and 3 SD over more than 3 months (CT and US), and in 1 CR, 4 PR, 1 MR and 1 SD of the tumor markers (n = 2 TM negative). Progression free survival in the imaging methods 5, 6, 6, 6, 9, >9, >10, >10, >12 months. Survival since beginning of therapy: >9, 10, >10, 11, >11, >12, >12, >12, >16 months. As in studies with Mitomycin-C + Gemcitabine (R. Klapdor et al, J. Cancer Res Clin Oncol 124, 1998, R11) the relevant tumor markers, in most cases CA 19-9, more rapidly reflected tumor response and tumor relapse than the imaging methods, offering themselves as relevant parameters for control and evaluation of efficacy of palliative treatment regimens of pancreatic cancer in individual patients. Side effects: 2 allergic reactions about 5 months after beginning of treatment, in most cases transient neuropathy (grade I, II and II–III in 5, 2 and 1 cases).

Conclusions: The results offer a combination therapy with gemcitabine + oxaliplatin as a potentially active and well tolerated regimen for a phase II study.

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Local effect of cisplatin/epinephrine injectable gel on intrahepatic lesions of hepatocellular carcinoma (HCC)

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Purpose: To evaluate a novel intratumoral chemotherapy with cisplatin/epinephrine injectable gel (CDDP/epi gel) in patients with HCC. The gel formulation is designed to deliver high drug concentrations for extended periods.

Methods: Patients with histologically proven HCC with ≤3 tumors (≤7 cm maximum diameter, ≤200 cm^3 total volume) and no major vessel involvement or extrahepatic disease were enrolled. CDDP/epi gel (1 mL contains 4 mg CDDP, 0.1 mg epi) was administered with percutaneous intratumoral injection under ultrasound control. Up to 10 mL CDDP/epi gel was given 1×/wk for 4 treatments within 6 wk. Tumors were evaluated with magnetic resonance imaging (MRI) 2 wk before and after treatment to assess tumor necrosis as a marker of response. Hyperintense lesions depicted at the arterial phase of gadolinium-enhanced, turbo spin-echo T1-weighted sequence were considered viable tumors.

Results: Seven patients (12 intrahepatic lesions) for whom liver resection was contraindicated due to previous hepatectomy (1) or poor liver reserve (6) were treated. Before treatment, median tumor volume was 12.6 cm^3 (range 4–32 cm^3). After one or two cycles of CDDP/epi gel, MRI showed no viable tumor in 11 of 12 lesions and only 11% viable tumor in one. Side effects (in 36 treatment sessions) included fever (10), chills and rigor (4), abdominal pain (8), and nausea or vomiting (11); all were mild to moderate in severity and subsided with conservative management.

Conclusion: Initial evaluations by MRI suggest that intratumoral CDDP/epi gel appears effective in eradicating viable intrahepatic HCC. Further follow-up will determine the association of treatment-related tumor response, as measured by both MRI and 3-phase CT scans, and effect on patient survival or disease progression.