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Daily stereotactic ultrasound targeting for radiotherapy of upper abdominal malignancies: improvement of target setup

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Purpose: Development and implementation of a strategy to use a stereotactic ultrasound-targeting device (BAT, Nomos Corp., Sewickley, PA) to accurately align to IMRT target volumes in the upper abdomen. Assessment of the potential for improvement of daily target repositioning.

Methods and Materials: In 52 patients treated between 10/00 and 2/03 for cholangio ca (8), HCC (10), liver metastases (10), pancreatic ca (16), and other tumors (8), target volumes, organs at risk and vascular guidance structures were delineated in contrast enhanced CT datasets. Daily ultrasound targeting was performed during treatment positioning. CT contours of delineated organs and vascular guidance structures were superimposed onto axial and sagittal US images, and positional adjustments, indicated by the system, were performed. The capability to improve target setup was assessed by comparison of organ and fiducial position in treatment planning CTs with control CT studies after ultrasound targeting in the CT suite.

Results: A total of 637 BAT-alignments were performed (mean 22, range 3 to 36 per patient). Mean absolute shift from skin mark position was 3.2±4.0 (mean±SD), 4.1±4.7 and 3.2±4.3 mm in x, y and z-direction, respectively. Mean magnitude 3D correction vector was 7.6±7.1 mm. 35%, 14.3% and 3.5% of alignments were corrected by a magnitude of >10, >15, and >20 mm, respectively. Correlation of BAT targeting with alignment error in control CT in 15 patients revealed setup error reduction in 14/15 alignments. The sole worsening of initial setup was by a magnitude of

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Adjuvant chemo-radiotherapy with 5FU/FA/DDP/paclitaxel in locally advanced gastric cancer (UICC II-IV M0)

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Background: The survival benefit for chemo-radiotherapy observed in the adjuvant US intergroup study 0116 on gastric cancer prompted us to start a phase II trial testing the feasibility and efficacy of an intensified chemo-radiation schedule.

Methods: 70 patients entered the protocol since December 2000 and 42 evaluable patients have finished the treatment. Treatment consisted of 6x 5-FU 2000mg/m^2/24h, FA 500mg/m^2/2h weekly and paclitaxel 175mg/m^2 weeks 1+4 and cisplatin 50mg/m^2 weeks 2+5 followed by 45 Gy (5x 1.8 Gy/ week) radiotherapy of the gastric bed in combination with simultaneous 5-FU continuous infusion (FU 225mg/m^2/24h, weekend off) followed by second cycle of 5FU/FA/DDP/paclitaxel.

Results: The median age was 48 years. 56% underwent total gastrectomy, 57% D2 lymphatic resection, and 7% R1-resections. UICC stage IB, II, IIIA, IIIB, and IV M0 were observed in 4%, 36%, 27%, 9%, and 24% of patients, respectively. Toxicity grade III/IV: leukocytopenia 43%, neutropenic fever 5%, anorexia 9%, diarrhoea 4%. One death caused by pneumocystis carinii pneumonia. Only 2 of the grade III/IV toxicities (1x diarrhoea, 1x leukocytopenia) occurred during simultaneous chemo-radiotherapy. The dose intensity for 5FU/FA, paclitaxel, and cisplatin was 85%, 80%, and 80%, respectively. All patients received full dose radiotherapy. At a median follow up of 15 months the disease free survival was 94%.

Conclusions: This intensified adjuvant chemo-radiation regimen is feasible exhibiting tolerable toxicity and will be basis for a phase III trial. Updated results on 70 evaluable patients will be presented.

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Suppression of TGF-beta2 in pancreatic cancer by the antisense oligonucleotide ap 12009: preclinical efficacy data as basis for clinical studies

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As the most potent immunosuppressor known transforming growth factor beta (TGF-beta) plays a key role in advanced cancer as well as by regulating additional pivotal pathomechanisms such as metastasis, angiogenesis and tumor cell proliferation. With a 5-year-survival rate of less than 0.4% pancreatic cancer is one of the most aggressive cancers. Enhanced expression of TGF-beta correlates with decreased survival, the TGF-beta2 isoform is associated with advanced tumor stage. Aiming at a highly specific anti-tumor therapy AP 12009, a phosphorothioate antisense oligonucleotide specific for the human TGF-beta2 mRNA, has been developed. AP 12009 has already shown efficacy in phase I/II clinical studies as therapy for high-grade glioma: The overall median survival time was prolonged after temozolomide and subsequent AP 12009 therapy as compared to temozolomide therapy alone. One complete tumor remission was documented. Similar to the convincing preclinical data obtained in glioma cells TGF-beta2 secretion of several pancreatic cancer cell lines was significantly reduced by AP 12009. In functional assays AP 12009 was able to inhibit tumor cell proliferation in a dose-dependent manner by up to 73%. Migration of pancreatic cancer cells was blocked by AP 12009 as compared to controls in a spheroid migration model. Safety pharmacology of AP 12009 was assessed in cynomolgus monkeys. After short-term infusion no observed adverse effect levels (NOAEL) were between 5 - 20 mg/kg b.w. for complement activation, cardiovascular and clotting system and below 5 mg/kg b.w. for hematological parameters. Subchronic toxicity studies revealed a NOAEL of 1 mg/kg b.w./day for 4 weeks. Single intravenous bolus in mice and rats did not cause any toxic symptoms up to 100 mg/kg b.w. (LD50: 706 mg/kg b.w. for mice; 1,175 mg/kg for rats). A multi-site clinical phase I/II study with AP 12009 in pancreatic carcinoma is now in preparation. The clinical trials will initially focus on the tolerability of AP 12009 in pancreatic cancer patients and will be designed to assess the maximum tolerated dose (MTD).

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Fifteen-month registration of patients with digestive endocrine tumors (DET) in France (FFCD-ANGH-GERCOR study)

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The prevalence, clinical profiles and management of DET in France are not known. From 1st August 2001 to 31 October 2002, standardized records on patients with DET were prospectively completed in 87 participating centers. The total group amounted to 668 patients (pts) (sex ratio: 1.0, median age: 56 years (range: 12-89)), including pts presenting for the first time (27%) or for a second opinion (12%) and patients on follow-up (61%). The median delay between initial diagnosis and registration was 26 months (range: 0-423). WHO performance status was 0/1 for 80% of pts. The primary sites were the small bowel or colon (288, 43%), pancreas (211, 32%, of whom 14 had multiple endocrine neoplasia type 1), unknown (77, 11%), stomach (33, 5%), non digestive (24, 4%), appendix (20, 3%), rectum (12, 2%), and esophagus (3). A peptide secretion syndrome was present in 39% of pts. Most pancreatic tumors were non functional (72%). Metastatic disease was observed in 73% of pts. Metastases were synchronous in 74% of pts. Most tumors were well differentiated (86%). S omatostatin receptor scintigraphy was performed in only 55% of pts. Taking into account the entire disease courses, the respective figures for surveillance, surgery, chemotherapy, somatostatin analog, interferon, chemoembolisation and debulking of metastases were 37, 66, 41, 35, 12, 19 and 26%. Despite their low prevalence, DET represent a significant and heterogeneous clinical group. Most patients in this nationwide survey have well differentiated metastatic DET, which warrant the design of prospective therapeutic trials.