as a molecular marker for multiple gastric cancers, we examined MSI in patients with single gastric cancer and in patients with multiple gastric cancers. Materials and Methods: We examined MSI in 38 patients with single gastric cancer, in 26 patients with synchronous multiple gastric cancers, and in 12 patients with metachronous multiple gastric cancers (follow-up period: 12-54 months). In the patient with synchronous multiple gastric cancers, larger tumor was examined. In the patient with metachronous multiple gastric cancers, first gastric cancer was examined. Five microsatellite loci including D17S855, D18S58, D18S61, BAT25 and BAT40 were examined by microsatellite assay. Results: MSI at 1 or more loci was detected in 3 of 38 (8%) patients with single gastric cancer, in 7 of 26 (27%) patients with synchronous multiple gastric cancers, and in 4 of 12 (33%) patients with metachronous multiple gastric cancers. The frequency of MSI was significantly higher in the patients with multiple gastric cancers, both synchronous and metachronous,than in those with single gastric cancer ($P<0.05$). Patients with MSI(+) gastric cancer tended to develop secondary gastric cancer frequently, when compared with patients with MSI(-) gastric cancer . Conclusion: These data suggest that MSI may be used as a molecular marker to predict the development of multiple gastric cancers.

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Near-Infrared Fluorescent Somatostatin Receptor Analogs As Tracer Molecules For Tumor Diagnosis

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Background/Objective: Neuroendocrine tumors overexpress somatostatin receptors (SSTRs). SSTR scintigraphy using the radiolabeled somatostatin analog octreotide has been used for several years in the diagnosis of such tumors. We here report the synthesis and use of a peptide-dye conjugate consisting of a near-infrared fluorescent cyanine dye and the somatostatin analog octreotate as a new contrast agent for optical imaging. Methods: Receptor binding, internalization and subcellular localization of the dye conjugate were studied in SSTR2-transfected RIN38 insulinoma cells and human primary neuroendocrine cells by confocal laser microscopy. Flow cytometry was used for quantitation. Whole-body imaging of mouse xenografts was done to assess the conjugates in vivo. Results: Specific uptake of the ligand conjugate but not a control peptide was detected, receptor and dye-labeled ligand colocalized. In flow cytometry, indodicarbocyanine-octreotate produced a more than 500-fold increase in fluorescence intensity. Biodistribution of the conjugate was examined in vivo after intravenous injection into RIN38/SSTR2 tumor-bearing nude mice by laser-induced fluorescence whole-body imaging. In these animals, tumor fluorescence increased rapidly and was more than threefold higher than that of normal tissue from 3 to 24 hours after application. These results could be confirmed by fluorescence microscopy on tumor tissue sections of these mice. A control peptide-dye conjugate with 100fold lower affinity did not label tumor cells in vivo or in vitro. Incubation of primary cell cultures derived from human neuroendocrine tumors with the conjugate resulted in a internalization of the compound into the tumor cells but not into adjacent fibroblasts. Conclusion: Cyanine dye-labeled octreotate therefore is a promising receptor-targeted contrast agent for optical imaging. As many tumors overexpress peptide receptors, this new technique may help bridge diagnostic gaps also in other fields of oncology, especially in early detection of small lesions.

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Diagnostic Value of Plasma CgA in Neuroendocrine Tumors.

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Background The aim of this study was to assess the value of plasma chromogranin A (CgA), a protein produced by neuroendocrine cells, in the diagnosis of neuroendocrine tumors. Methods Eighty subjects with neuroendocrine tumors were studied. Thirty-four had carcinoids, 21 nonfunctioning endocrine pancreatic tumors, 17 multiple endocrine neoplasia type 1 (MEN 1) (6 of these also had gastrinomas), and 8 had functioning pancreatic tumors (4 gastrinomas, 2 glucagonomas, 2 somatostatinomas). Twenty-eight healthy subjects were studied as controls. A fasting plasma sample was obtained from each subject, and CgA plasma levels were measured by means of the ELISA method using a kit (Dako A/S, Denmark). Results In controls subjects, plasma CgA values were below 5 U/L. Among the patients, 20 of the 34 with carcinoid tumors, 12 of the 21 with nonfunctioning pancreatic tumors, 9 of the 17 with MEN 1 (including the 6 with gastrinomas) and the 4 gastrinomas of the 8 functioning pancreatic tumors on the whole 45 out of the 80 patients, 56.3%, had abnormally high CgA values (22-961 U/L). Most of the patients with elevated CgA values, except 9 of the 10 with gastrinomas had multiple liver metastasis. Conclusions The results shown that the diagnostic value of plasma CgA in neuroendocrine tumors is relatively low. It may have some interest only in patients with advanced disease and liver metastasis. Gastrinoma seems to be an exception, since in this tumor high CgA values are generally found even in the absence of liver metastasis.

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^{18}Fluor-DOPA Whole-Body Positron Emission Tomography for Detection of Neuroendocrine Gastrointestinal Tumors

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Background: Imaging of neuroendocrine gastrointestinal tumors is often difficult. In the present study we evaluated ^{18}F DOPA positron emission tomography (PET) as a new diagnostic procedure. *Methods:* After studying the normal distribution of ^{18}F DOPA, 17 patients with histologically confirmed manifestation of a neuroendocrine gastrointestinal tumor were examined using ^{18}F DOPA PET. Results of ^{18}Fluordeoxyglucose (FDG) PET, somatostatin-receptor scintigraphy (SRS) and morphological imaging procedures (CT/MRT) were available for all patients. All individual procedures were evaluated without prior information. Data assessment was made in cooperation of experienced radiologists and specialists in nuclear medicine for each patient based on all findings available. This cooperation served as gold standard individual procedures were compared with. *Results:* A total of 92 tumor manifestations was diagnosed (8 primary tumors (PT), 47 lymph node metastases (LNM) and 37 organ manifestations (OM). The ^{18}F DOPA PET delivered 60 true positive findings, SRS 52 (4 PT, 27 LNM, 21 OM) and the morphological imaging 67 (2 PT, 29 LNM, 36 OM). The following overall sensitivities were observed: ^{18}F DOPA PET 65%, ^{18}FDG PET 29%, SRS 57%, morphological procedures 73%. Thus, the morphological procedures produce the best overall results with a particular superiority as concerns organ metastases. With respect to primary tumors and lymph node staging, the best results were obtained with ^{18}F DOPA PET. Interestingly, nearly all serotonin-expressing tumors accumulated the radiopharmaceutical. *Conclusion:* Thus, ^{18}F DOPA PET is a promising new procedure for diagnostic imaging of neuroendocrine gastrointestinal tumors. ^{18}F DOPA PET is superior to other methods as concerns the visualisation of primary tumors and lymph node metastases. Moreover, our data indicate that no single procedure provides adequate diagnostic certainty and therefore we suggest that morphological tomographic imaging should be combined with ^{18}F DOPA PET.

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A Prospective Comparison of Fluorescence In Situ Hybridization (FISH) and Routine Cytology (RC) for the Identification of Malignancy in Biliary Tract Strictures

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FISH is a sensitive method of detecting aneuploidy in malignant cells. We have developed a FISH technique using probes from chromosomes 3,7 9 and 17, which selectively detects aneuploidy. This technique is especially useful when analyzing specimens with sparse cellularity such as bile or endoscopic brushings. Methods: Consecutive patients undergoing endoscopic retrograde cholangiography for suspected biliary strictures were enrolled in a prospective study comparing the accuracy of FISH and RC. We report here the results of the first 13 patients in this ongoing study. Bile was collected when possible from a cannula placed in the distal bile duct prior to injection of contrast at ERCP. Standard brush cytology sampling was performed twice using two cytology brushes per patient. Both brushes were fixed in a single specimen vial. The specimen was divided into two samples for evaluation by FISH and RC. FISH was performed by a technician and pathologist blinded to the clinical findings and RC results. A mixture of fluorescent labeled probes to the centromeres of chromosomes 3, 7 and 17, and band 9p21 (P16/CDKN2A gene) were used for FISH to assess cells for chromosomal abnormalities indicative of malignancy. Strictures were classified as malignant or benign based on clinical findings. Results: (Table) Five of 12 strictures were malignant. FISH revealed aneuploidy in 3 of 5 malignant lesions while RC failed to revealed malignancy. All benign strictures were classified as negative by FISH and negative by RC. Conclusions: 1.Based upon preliminary data, ploidy determination by FISH is useful in identifying malignant biliary tract strictures and may be superior to RC. 2. The study is ongoing and additional data will be presented.

# of Specimens Correctly Classified

Diagnosis (n)	RC	FISH
Cholangio CA (2)	0	1
Pancreatic CA (3)	0	2
PSC (5)	5	5
Chr Pancreatitis (1)	1	1
Idiopathic (1)	1	1

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Comparison of the ARMS and ASO Test for K-ras Mutations with Cytology on Endobiliary Brushes from 312 Patients with Extrahepatic Biliary Stenosis.

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Background Benign and malignant diseases can cause extrahepatic biliary stenosis (EBS). The sensitivity of biliary cytology for a malignant cause is relatively low. K-ras mutational analysis on brush cytology is a valuable adjunct, but the specificity remains a concern. A quantitative test for K-*ras* mutations (ARMS) has been developed. The additional diagnostic value and the test characteristics to increase specificity were assessed. Methods Brush samples obtained during ERCP were prospectively collected from 312 patients with EBS. A new