to measure functional changes in the liver that result from the development of liver metastases. Over the last nine years, in a series of animal and clinical experiments, we have demonstrated that the presence of tumour within the liver causes changes in the hepatohaemodynamics with alterations both in hepatic arterial and portal flow. These changes appear to be the result of the release of a vasoactive agent although this has not yet been identified.

In patients hepatic and portal venous inflow can be measured indirectly using scintographic methods or more recently by direct measurements using colour Doppler flowmetry. Using both of these techniques, we are able to predict the development of liver metastases in patients undergoing curative colorectal surgery who have no metastases apparent at the time of surgery assessed by either computerised tomography or ultrasound techniques. These measurements independently predict prognosis for a patient and may be useful in selecting high risk cases for adjuvant chemotherapy.

1006
PROGNOSTIC FACTORS INFLUENCING SURVIVAL AFTER SURGICAL TREATMENT

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Liver metastases (LM) are still a main problem in oncology. While diagnosis is easily performed today, prevention and treatment are still difficult. Surgical approach can be technically performed in about 10% of the cases with LM. A classification should be used to evaluate results. Prognostic factors analysed are: primary stage, relapse time and preoperative CEA value, number and the site of M, surgery type, stage according to system we propose and in some cases cell biology of both primary and secondary tumours. No significant statistical differences are observed for sex, age, primary stage, surgery type and extent of liver involvement are important prognostic factors. Multivariate analysis was performed considering data primary stage, stage of M, surgery type and extent of liver involvement, the parameter where some significant P value was observed. The main prognostic factor is primary stage followed by stage of liver disease.

1007
NEW TRENDS IN THE TREATMENT OF LIVER METASTASES— REGIONAL CYTOSTATIC AND CYTOKINOTHERAPY

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The concept of regional infusion or perfusion therapy of liver malignancies has been known for many years but has never gained wide acceptance—mainly due to lack of prospective randomized trials.

Recently one randomized study has identified a significantly prolonged survival for patients subjected to temporary hepatic artery occlusion followed by intraportal 5-fluorouracil and oral allopurinol compared to a no treatment group.

One "phase I" study has shown that isolated regional perfusion of the liver with hyperthermia and cytostatic drugs is feasible. An ongoing phase I study with a similar design plus TNF-α is under way. Preliminary results show an effect on sarcomas and melanomas.

More prospective studies evaluating regional therapy are warranted.

1008
NEW SURGICAL AND COMBINED MODALITY APPROACHES TO COLORECTAL LIVER METASTASES

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To improve the results of surgery in the treatment of liver metastases the following strategies are under investigation:

1. Adjuvant systemic and regional chemotherapy to eliminate micrometastases
2. Preoperative intraarterial chemotherapy to improve resectability and to avoid intraoperative tumour cell propagation
3. Intraoperative sonography as well to improve the definition of adequate resection margins as to detect additional metastases
4. Radio-Immuno-Guided Surgery (RIGS) or Laser-Induced-Fluorescence-Diagnosis (LIFD) to improve the intraoperative detection of micrometastases and of extrahepatic tumour manifestations
5. Laser-Induced-Hyperthermia (LIT) or cryotherapy to treat irresectable metastases
6. *In situ* or *ex situ* liver perfusion (work bench technique) to treat multiple liver metastases
7. Tumour cell vaccination to treat colorectal micrometastases

These strategies will have to be approved in further, carefully planned clinical investigations. There is hope that at least some of these concepts will add to a stepwise improvement of the results of surgical therapy in patients with colorectal liver metastases.

1009
REGIONAL TREATMENT OF LIVER METASTASES BY EXTENSIVE SURGERY AND HIGH DOSE CHEMOTHERAPY

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Liver resection for colorectal liver metastases has changed dramatically in recent years. Better preoperative diagnosis and surgical techniques have improved the possibilities of this therapy with long-term survival and disease-free survival rates of 35 and 25% respectively. Also repeat liver resections can be performed with safety and good long term survival results. Unfortunately the majority of patients are not candidates for resection and systemic chemotherapy leads to responses in at the most 15% of patients. Hepatic arterial infusion has increased response rates but with few complete responses in the liver. We developed a recirculation perfusion of the vascularly isolated liver. At a dose of 3.0 mg/kg L-PAM was able to have a response in all patients with a considerable number of complete responses in this ongoing study. An update of the clinical results, the role of the tripeptide thiol glutathione (GSH) and future other applications of this technique will be presented. Clinicians should realize that in treating patients with liver metastases the only way to achieve survival benefit is to treat aggressively or not at all.

1010
CONTROL OF INVASIVE CELL GROWTH BY RECEPTORS OF THE HGF FAMILY

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The HGF receptor family includes tyrosine kinases encoded by three oncogenes: *MET*, *Sea* and *RON*. The ability to promote uncontrolled proliferation represents only one of the two facets of their oncogenic potential. The three members of the HGF receptor family share a unique functional feature: they mediate cell motility in physiological conditions, and invasiveness in their activated versions. This suggests a role in tumorigenesis and in progression to the metastatic phenotype. The $p190^{MET}$ receptor is a heterodimer of two (α β) disulfide-linked protein subunits. Two receptor isoforms, carrying a native ligand binding domain but lacking the kinase domain, arise from alternative post-transcriptional processing. In physiological conditions, HGF binding triggers tyrosine autophosphorylation of its receptor, upregulating its kinase activity: site-directed mutagenesis of two tyrosine residues involved in the positive regulation of the catalytic activity (Y^{1234} or Y^{1235}) strongly impairs the transforming potential of the oncogenic counterpart of the receptor. Negative regulation of the kinase activity occurs through distinct pathways involving protein kinase C or increase in the intracellular Ca^{2+} concentration. Receptor autophosphorylation of a multifunctional docking site, made of the duplicated degenerate sequence YVH/NV, mediates interactions with multiple SH2-containing signalling molecules, including PI 3-kinase, phospholipase-C-γ, $pp60^{c-Src}$, and the GRB-2/SoS complex. Mutation of the two tyrosines (Y^{1349} and Y^{1356}) of the bidentate docking site results in the abrogation of the transforming activity in the oncogenic counterpart of the receptor.

The *MET* oncogene is overexpressed (activated) in a significant fraction of human cancers, including thyroid and colorectal carcinomas. *MET* amplification is found in metastases. Cells transfected with the *MET* proto-oncogene display a motile and invasive phenotype in the presence of HGF. Recently we have identified the ligand for another member of the *MET* family, the *RON* receptor. We have shown that *Ron* is activated upon binding MSP (Macrophage Activating Protein), an HGF-like polypeptide involved in cell proliferation and chemotaxis.