From Chronic Inflammation to Cancer

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Abstracts
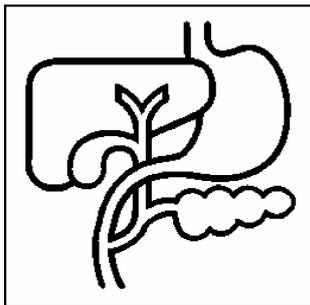## Poster Abstracts

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FROM CHRONIC INFLAMMATION TO CANCER

Brno (Czech Republic)
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CONTENTS

Gastric cancer

Colorectal cancer

Poster Abstracts

1. 5-Aminosalicylic acid induced multisystem disorders in the course of Crohn's disease
E. Akbal, S. Köklü, E. Kocak, B. Cakal, F. Kilic (Ankara, TR)

2. HER-2/neu - Protein marker of poor prognosis in gastric cancer
J. Ananiev, M.V. Gulubova, I.M. Manolova (Stara Zagora, BG)

3. Pancreatic cancer in patients with sporadic pancreatitis: Incidence and risk factors
A.F. Barbu, S.T. Barbu, I. Lupu (Cluj-Napoca, RO)

4. Progression of pancreatic intraepithelial neoplasia to invasive adenocarcinoma in chronic pancreatitis patients
S.T. Barbu, I. Domsa, A. Zolog, M. Cazacu (Cluj-Napoca, RO)

5. Gastric serrated adenoma polyp treated with endoscopic band ligation
O. Basar, S. Köklü, E. Akbal, M. Ibis (Ankara, TR)

6. Pseudotumoral proctitis associated with the long-term use of diclofenac suppositories
A. Berecz, D. Berecz (Odorheiu Secuiesc, RO)

7. IL-23 is a key pathogenic inducer of chronic intestinal inflammation
U. Billmeier, M.F. Neurath, S. Wirtz (Erlangen, D)

8. Screening of patients with Crohn's disease (CD) and ulcerative colitis (UC) for malnutrition is a MUST
I. Chermesh, T. Mashiach, A. Karban, R. Eliakim (Haifa, IL)

9. Chronic pancreatitis and pancreatic cancer - Mortality risk factors
O.P. Ciof, A. Tudora, I. Sporea (Timisoara, RO)

10. The lymphoid aggregates and the bile duct lesions in chronic hepatitis C patients
D. Damian, M. Grigorescu, T. Zaharie, M.D. Grigorescu (Cluj-Napoca, RO)

11. Hepatic steatosis and chronic hepatitis C
D. Damian, M. Grigorescu, T. Zaharie, T. Mocanu (Cluj-Napoca, RO)

12. The necroinflammatory activity and the hepatic fibrosis in patients with chronic hepatitis C
D. Damian, M. Grigorescu, M.D. Grigorescu, T. Zaharie, T. Mocanu
(Cluj-Napoca, RO)

13. Palliative treatment of hepatocellular carcinoma in Romania
D.N. Dascalu (Sibiu, RO)

14. Trends of primary and subsequent cancers of gastrointestinum in the Czech population
P. Díte, E. Geryk, L. Pecen (Brno, CZ)

15. Overexpression of a splice variant of Smurf2 in T-cells upregulates the TGF-beta signalling pathway and protects mice from experimental colon cancer
H. Dornhoff, C. Becker, M.F. Neurath (Erlangen, D)

16. The importance of anti-dsDNA antibody in autoimmune hepatitis/primary biliary cirrhosis overlap syndrome
C. Efe, T. Purnak, E. Ozaslan (Bitlis, Ankara, TR)

17. An ultrastructural study of hepatic stellate cells in relation to carcinogenesis in patients with hepatitis C virus infection
N. Elkhafif, S. Mansy, H. Yehia, A. Abd el Fatah, I. Mostafa, N.M. El Assaly (Giza, ET)

18. Prediction of clinical outcome in chronic hepatitis due to HCV genotype 4 after combination therapy with pegylated interferon α-2a and ribavirin
N. Elkhafif, N.M. El Assaly, N. El Ashri, O. El Bendary, S.M. Shendy, M.A. Saber, E. El Dabaa (Giza, ET)

19. IBD: Molecular markers in diagnosis of colorectal cancer
O.V. Fedorova, E. Fedulova, O. Tutina, G.V. Medyantseva (Nizhny Novgorod, R)

20. Morphological predictors of cancer degeneration in ulcerative colitis
E. Fedulova, P. Potehin, O. Fedorova, O. Tutina (Nizhny Novgorod, R)

21. Ultrastructural and COX-2 immunohistochemical assessment of longstanding ulcerative colitis-related dysplasia
O. Fratila, C. Craciun, D. Dumitrascu, R. Mihaila, M. Puscasiu (Oradea, Cluj-Napoca, Sibiu, RO)

22. Contribution of hepatitis C virus infection to development of hepatocellular carcinoma
A. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut (Craiova, RO)

23. Analysis of development of gastric cancer in patients with Helicobacter pylori eradicated comparative with never infected patients
A. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut (Craiova, RO)

24. Colorectal polyps carcinogenesis - Possible risk factors
A. Goldis, D. Lazar, R. Goldis, A. Muresan, S. Taban, V. Lungu, V. Danila (Timisoara, RO)

25. Epidemiological trends of inflammatory bowel diseases (IBD) in the west part of Romania
A. Goldis, D. Lazar, I. Ratiu, M. Ionita, D. Koukoulas, A. Muresan (Timisoara, RO)

8

26. Prognostic significance of the clinicopathological factors in gastric cancer
R. Goldis, A. Goldis, D. Lazar, S. Taban, A. Muresan, A. Dema, M. Cornianu, I. Ratiu, E. Lazar (Timisoara, RO)

27. Development of colonic cancer - Possible risk factors
R. Goldis, A. Goldis, D. Lazar, A. Muresan, V. Lungu (Timisoara, RO)

28. Transforming growth factor-beta 1 promoter polymorphism, colorectal cancer susceptibility and prognosis
M.V. Gulubova, I.M. Manolova, L. Miteva (Stara Zagora, BG)

29. Helicobacter pylori infection and expressions of EGF, EGFR and c-erB-2 proteins in gastric carcinoma
K. Guzinska-Ustymowicz, A. Pryczynicz, M. Sokolowski, J. Czyzewska, V. Dymicka-Piekarska, D. Cepowicz, B. Kedra, A. Kemona (Bialystok, PL)

30. COX-2 and p53 correlations in chronic inflammation leading to dysplastic changes in longstanding ulcerative colitis
T. Ilias, O. Fratila, D. Puscasiu, A. Maghiar, T.T. Maghiar (Oradea, RO)

31. From chronic mixed infection to cancer: Case Report
M. Kanashvili, M. Makhviladze, N. Rukhadze, T. Kuchuloria, B. Kanashvili, S. Gogichaishvili, N. Okrostsvaridze (Tbilisi, GEO)

32. Fluorescence *in situ* hybridization biomarkers of gastric cancer risk in intestinalized *Helicobacter pylori* pangastritis
B.W. Kim, M.P. Bronner (Seoul, ROK; Cleveland, USA)

33. Implication of Notch signaling and CDX-2 expression in Barrett's carcinogenesis
P. Konturek, G. Burnat (Saalfeld, Erlangen, D)

34. Laparoscopic gastric GIST resection
R. Kotán, J. Pósán, L. Sasi Szabó, P. Sápy, L. Damjanovich, Z. Szentkereszty (Debrecen, H)

35. Prognostic significance of the cyclooxygenase-2 (COX-2) immunohistochemical expression in gastric cancer
D. Lazar, S. Taban, E. Lazar, A. Dema, M. Cornianu, I. Ratiu, A. Goldis, I. Sporea (Timisoara, RO)

36. Hepatic carcinoma as outcome of natural course of liver cirrhosis
B.N. Levitan, E. Popov, G. Levitan (Astrakhan, R)

37. Clinical utility of red cell distribution width (RDW) in active inflammatory bowel disease
V. Licul, B. Mijandrusic Sincic, I. Mikolasevic, S. Milic, D. Stimac (Rijeka, HR)

38. Role of *CD24* polymorphisms in the susceptibility to inflammatory bowel disease
V. Lisiansky, M. Moshkowitz, I. Naumov, D. Kazanov, L. Galazan, S. Kraus, M. Leshno, N. Arber (Tel Aviv, IL)

39.   Increased tissue levels of transforming growth factor-beta 1 in patients with advanced colorectal cancer
       I.M. Manolova, M.V. Gulubova, J. Ananiev (Stara Zagora, BG)

40.   Adenosine deaminase activity and its isoenzymes in patients with Crohn's disease
       I. Maor, T. Rainis, A. Lanir, A. Lavy (Haifa, IL)

41.   Gene expression and genetic polymorphisms in TLR4 and COX-2 genes in inflammatory bowel disease and colorectal adenomas
       A. Ocepek, P. Skok, U. Potocnik (Maribor, SLO)

42.   Acute seronegative autoimmune hepatitis
       E. Ozaslan, U. Samsar, E. Erden (Ankara, TR)

43.   Intestinal lymphoma in a patient with Crohn's disease - Is there any interdependence?
       O. Petrascu, M. Deac, R.G. Mihaila, A.B. Boicean (Sibiu, RO)

44.   Diabetes mellitus and pancreatic cancer: A case-control study in Albania
       S. Prifti, B. Kraja, M. Sina, N. Dhigoi, I. Akshia (Tirana, AL)

45.   Fas/FasL expression in IBD and colorectal cancer
       A. Pryczynicz, K. Guzinska-Ustymowicz, M. Sokolowski, J. Czyzewska,
       V. Dymicka-Piekarska, D. Cepowicz, B. Kedra, A. Kemona (Bialystok, PL)

46.   Myeloperoxidase (MPO-463) gene polymorphism in the pathogenesis of gastric and duodenal ulcers
       A. Prystupa, K. Król, G. Dzida, J. Mosiewicz (Lublin, PL)

47.   PCNA and VEGFR expression in colon cancer prognosis
       C. Searpe, V. Sbarcea, L. Mogoanta, M. Tenovici, M. Searpe (Craiova, RO)

48.   The implication of Helicobacter pylori infection, anti-parietal cell antibodies and cytokines in the degree of atrophic gastritis
       C.A. Silosi, I. Silosi, V. Biciusca, O. Drackoulogona (Craiova, RO; Patra, GR)

49.   The total gastrectomy in gastric cancer
       C.A. Silosi, I. Silosi (Craiova, RO)

50.   Considerations in the immunohistochemical diagnosis of malignant soft tissue tumors of mesenchymal origin
       I. Silosi, C.A. Silosi, V. Biciusca (Craiova, RO)

51.   Colorectal malignancies and chronic inflammation in UC: Is JC virus involved?
       D. Stoyanova, I. Tsekov, D. Dardanov, K. Katzarov, G. Kirov, Z. Kalvatchev
       (Sofia, BG)

52. Laboratory testing of sera after precutan drainage of the sterile peripancreatic fluid in patients with acute pancreatitis
Z. Szentkereszty, R. Kotán, J. Pósán, L. Sasi Szabó, P. Sápy, S. Sipka, L. Damjanovich (Debrecen, H)

53. An unusual metastasis from a primary colonic adenocarcinoma
S. Taban, A. Dema, E. Lazar, M. Cornianu, D. Lazar, E. Cev (Timisoara, RO)

54. Incidence of constipation, ulcerative colitis and colorectal cancer in Dushanbe
M.S. Tabarov, N.A. Nuriloeva, Z.M. Toshtemirova, K. Shemerovsky (Dushanbe, TAD; St. Petersburg, R)

55. Long-term follow-up and risk for colorectal cancer in patients with ulcerative colitis from Moldova
S. Turcan, V. Dumbrava, R. Tanase, S. Barca (Chisinau, MOL)

56. Dysplasia and the risk for colorectal cancer in ulcerative colitis
V. Vacariu, C. Banciu, I. Romosan, N. Tudose, E. Potencz (Timisoara, RO)

57. Gastric cancer in elderly patients
V. Vacariu, C. Banciu, I. Romosan, L. Susan, I.A. Szucsik (Timisoara, RO)

58. Analyzing the role of mucosal mast cells inducing colitis-associated colorectal cancer (CRC)
B. Weigmann, M. Stassen, C. Taube, M.F. Neurath (Erlangen, Mainz, D)

59. Both MGMT- and AAG-dependent DNA repair mechanisms protect against inflammation-dependent colon carcinogenesis
S. Wirtz, G. Nagel, L. Samson, B. Kaina, M.F. Neurath
(Erlangen, Mainz, D; Cambridge, USA)

60. Epithelial STAT3 links chronic intestinal inflammation to colon cancer
N. Wittkopf, G. Pickert, C. Neufert, M. Leppkes, M. Warntjen, H.-A. Lehr, S. Hirth, B. Weigmann, S. Wirtz, M.F. Neurath, C. Becker
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Session I

Chronic inflammation

Inflammation and immunity in the tumor microenvironment

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Chronic and persistent inflammation contributes to cancer development and can predispose to carcinogenesis. In 1863 Rudolf Virchow noted leukocytes in neoplastic tissues and described a connection between inflammation and cancer. He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Over the past years many reports supported Virchow's hypothesis. The links between cancer and inflammation are starting to have implications for prevention and treatment.

Hallmarks of cancer-associated inflammation include the presence of infiltrating leukocytes, cytokines, chemokines, growth factors, lipid messengers, and matrix-degrading enzymes. Schematically, two interrelated pathways link inflammation and cancer. (1) Genetic events leading to neoplastic transformation promote the construction of an inflammatory milieu. (2) Tumor infiltrating leukocytes are prime regulators of cancer inflammation. If genetic damage is the "match that lights the fire" of cancer, some types of inflammation may provide the "fuel that feeds the flames". The microenvironment of a tumor is an integral part of its physiology, structure, and function. A fundamental deranged relationship between tumor and stromal cells is essential for tumor cell growth and progression.

Tumor-associated macrophages are a major component of the leukocyte infiltrate of most tumors. There is a dual potential of these macrophages. They can kill tumor cells or elicit tissue destructive reactions. However, macrophages can stimulate tumor-cell proliferation, promote angiogenesis, and favor invasion and metastasis. It is suggested that tumor-associated dendritic cells are immature reflecting lack of effective maturation signals. Therefore, dendritic cells in tumors are poor inducers of effective response of lymphocytes to tumor antigens. In tumors the predominant T-cell population has a "memory" phenotype. There cytokine repertoire has not been studied systematically but in some tumors they produce mainly Th2 type cytokines. Besides inflammatory cells, tumor stroma consists of new blood vessels, connective tissue, and a fibrin-gel matrix. Many factors produced by tumor cells promote tumor angiogenesis and generation of extracellular matrix. The cytokine network of tumors is rich in inflammatory cytokines, growth factors, and chemokines but generally lacks cytokines involved in specific and sustained immune responses. There is now evidence that inflammatory cytokines and chemokines, which can be produced by the tumor cells and the tumor-associated leukocytes and platelets, may contribute directly to malignant progression. High-dose local tumor necrosis factor selectively destroys tumor blood vessels, but when chronically produced this cytokine may act as an endogenous tumor promoter, contributing to the tissue remodelling and stromal development necessary for tumor growth and spread. In addition, tumor cells have co-opted some of the signalling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis.

The causal relationship between inflammation, innate immunity and cancer is widely accepted. However, many of the molecular and cellular mechanisms mediating this relationship remain unresolved. Investigations regarding the link between inflammation and cancer would be vital for identifying cell or protein targets for cancer prevention and therapy.

Oxidative stress and iNOS induction in carcinogenesis

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Reactive oxygen species (ROS) have been implicated in a number of pathologies, including inflammatory diseases of the gastrointestinal tract, alcoholic liver disease, and several other types of toxic liver injury. ROS production within the cells is controlled by numerous antioxidant intracellular defence mechanisms, which include superoxide dismutase, catalase, glutathione peroxidase and ascorbic acid. However, under certain conditions, ROS overproduction may exceed the cellular defences and damage the intracellular macromolecules, including nucleic acids (DNA and RNA). ROS attack to DNA causes the production of stable covalent bonds and the subsequent formation of potentially mutagenic and carcinogenic DNA adducts.

Considerable data suggest that ROS may also play a pathogenic role in carcinogenesis. In the initiation/promotion phase of this process, ROS can either interact directly with genomic DNA, damaging, among others, specific genes that control cell growth and differentiation, or increase the activity of carcinogenic xenobiotics. ROS may also stimulate growth of malignant cells in the progression phase of carcinogenesis. The most damaging species among the many ROS is the hydroxyl radical. The hydroxyl radical has been shown to be responsible for a number of base modifications that include thymine glycol, thymidine glycol, 5-hydroxylmethyluracil and also 8-hydroxydeoxyguanosine (8-OHdG). 8-OHdG is a modification of guanine that induces a point mutation in the daughter DNA strands and that is consequently used as an index of DNA damage. The identification of 8-OHdG stimulated a number of studies attempting to investigate the possible relationship between oxidative DNA damage and carcinogenesis. Studies using DNA templates containing 8-OHdG indicate that this oxidatively modified residue persists, accumulates in cell DNA and causes mispairing, thus suggesting that this lesion is mutagenic and therefore potentially carcinogenic.

Although it is well known that ROS induction lies at the center of a complex network of tissue and inflammatory responses involving the expression of cytokines, growth factors and oncogenes, this network has not been thoroughly investigated in HCV-related liver disease.

The mechanisms driving hepatic damage and hepatocarcinogenesis are complex and involve both host and viral factors. During virus-related disease, both in humans and experimental models, an increased production of ROS has been documented, with a strong link between HCV core protein and HBV X protein and oxidative "burst", in particular in the first phases of carcinogenesis.

Oxidative damage and telomerase activity
Cells that are not able to start the process of apoptosis, in particular after DNA damage, can be more susceptible to genetic alterations and to acquire immortality through the modulation of telomerase activity. Telomerase activation is very important for cell proliferation, senescence, immortalization and carcinogenesis. Telomerase, a RNA-dependent DNA polymerase, is a complex ribonucleoprotein composed by two components, a catalityc subunit (hTERT) and a RNA component complementary to telomeric sequences (hTR). Telomerase, after retrotrascription of

its own RNA, adds telomeric sequences to chromosomic terminal portions, mantaining invariate the length of telomeres, whose main function is to stabilize chromosomic structure. Telomeres, however, at each replication cycle become shorter and when they reach a critical lenght (telomeric crisis), they lose their function. In some cells, the substantial shortening of telomeres results in end-to-end fusions during cell cycle. Following this, somatic cells stop proliferation cycle and go in senescence and apoptosis. In neoplastic cells telomeric shortening is avoided by the increased telomerase function and so cells can escape senescence and apoptosis. Telomere shortening and chromosomic instability happen in the first phases of carcinogenesis, while the tumor progression is linked to telomeric preservation likely induced by a restarting of telomerase activity. In fact only cells that find a way to mantain telomere lenght, allowing illimitated cell divisions, with a certain chromosomic instability degree, have an higher risk of neoplastic transformation and will be able to advance to cancer.

Our recent data show that telomeres length and telomerase activity can be modulated by ROS-induced oxidative stress. In fact telomeres, rich in guanines, are highly sensitive to ROS attack, in particular by hydroxyl radical. ROS interaction with telomeric sequences creates DNA adducts as 8-hydroxydeoxyguanosine. This could be a possible mechanism by which oxidative stress can accelerate telomeric shortening. Besides, unlike in most genomic DNA, DNA repair mechanisms of telomeric DNA are less efficient and so telomeres accumulate oxidative damage. Consequently, measuring telomeres lenght could be a very good biomarker of chronic oxidative stress.

Oxidative damage, cytoproliferation and apoptosis

Cancer development requires the acquisition of several capabilities that include increased replicative potential, anchorage and growth-factor independence, evasion of apoptosis, angiogenesis, invasion of surrounding tissues and metastasis. It was suggested that the development of cancer is the result of a loss of balance between an abnormal cellular mitotic rate and apoptosis. Both extrinsic (TNF-α, Fas/FasL, TGF-β,) and intrinsic (pro- and anti-apoptotic Bcl-2 family members, BI-1 and NF-κB) mediators are involved in the activation of the apoptotic process. Analysis of mRNA transcripts and the corresponding proteic products, in the tissues with different degree of liver damage seems to be the best strategy for carcinogenesis studies.

Oxidative damage and miRNA

Recently, the important role of MicroRNAs (miRNAs), a non-coding family of genes involved in post-transcriptional gene regulation, in cell proliferation, differentiation, cell death and carcinogenesis has been reported. The miRNA 122 for instance is specifically expressed in the human liver and has been shown to interact with the 5'non-coding region of HCV genome. Several others miRNAs however have been identified, whose expression is modulated in hepatocellular carcinoma, again also during oxidative damage. In particular, our data demonstrate that mir-199a, mir-199b, mir-195 and mir-122a were strongly downregulated in the majority (55–70%) of HCCs, while mir-92 and mir-145 showed a less marked downregulation. In contrast mir-222 was upregulated in the HCC. Additionally, in HCC tissues, a significant positive correlation was found between microRNA-92 expression, already linked to hepadnavirus-associated carcinogenesis, c-myc, frequently activated in HCC, and 8-OHdG levels.

18

Oxidative damage and iNOS

Inducible nitric oxide synthase (iNOS) produces sustained nitric oxide (NO.) concentrations in response to proinflammatory agents. NO is a major mediator of chronic inflammation and may modulate tumorigenesis by regulating cell proliferation, survival, migration, angiogenesis, drug resistance and DNA repair. Results suggest that oxidative and nitrative DNA damage occurs at the sites of carcinogenesis, regardless of etiology. Therefore, it is considered that excessive amounts of reactive nitrogen species produced via iNOS during chronic inflammation may play a key role in carcinogenesis also by causing DNA damage.

Several authors found a progressive iNos induction in rat and mouse liver lesions, with higher levels found in the most aggressive models, such as in HCC induced in rats genetically susceptible to hepatocarcinogenesis and in c-Myc-TGF-α transgenic mice. iNOS was significantly higher in HCC with poorer prognosis (as defined by patients' survival) and were positively correlated with tumor proliferation, genomic instability, microvascularization, and negatively with apoptosis.

Role of COX in pathogenesis and prevention in the development of GI tumors

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Colorectal cancer (CRC) is a major health concern world-wide. In 2010, it is estimated that more there will be more than 1,000,000 new cases, half of them are going to die. The limited success of current treatments for most advanced common malignancies highlights the importance of cancer prevention.

Chemoprevention is an emerging science that involves the long term use of a variety of oral agents that can delay, prevent or even reverse the development of adenomas in the colon. Recent observations suggest a number of potential targets for chemoprevention. Many agents including folic acid, calcium, estrogen, vitamins, olpitraz, ursodiol and fiber have shown a great deal of promise, but only modest chemopreventive efficacy in clinical trials. The most promising drugs are aspirin and the NSAIDs. NSAIDs are potent inhibitors of the COX enzymes.

There are two isoforms of the COX enzymes. COX-1 is constitutively expressed in normal tissues and serves as a 'housekeeper' of mucosal integrity, while COX-2 is an immediate early response gene that is highly inducible by neoplastic and inflammatory stimuli. COX-2 is significantly over-expressed in colorectal neoplasms, making it an attractive therapeutic target.

The preventive efficacy of this class of agents is supported by more than 200 animal studies. A proof of concept in humans was achieved in familial polyposis patients. Most significantly, in 57 epidemiological studies (out of 59) it was clearly demonstrated that NSAIDs consumption prevents adenoma formation, decrease the incidence of CRC and even reduce the mortality from CRC. NSAIDs consumption is not toxic-free. Figures in 1997 showed 107,000 hospitalizations and 16,500 deaths in the US alone as a result of NSAIDs and aspirin consumption, equaling the mortality from AIDS or leukemia.

COX-2-specific inhibitors, which should have an improved safety profile, are an ideal drug candidate for the prevention of CRC, since increase expression of COX-2 is seen through all stages of the multi-step process of CRC carcinogenesis.

Three International, multicenter, prospective, randomized, placebo-controlled and trials in the secondary prevention of CRC were launched in the years 1999 and 2000. These clinical trials using cyclooxygenase (COX) inhibitor drugs demonstrated the potential of chemoprevention as a strategy for reducing cancer incidence, although not without associated side effects. The attractiveness of these drugs partly stems from an ability to engage multiple mechanisms of action by their potential to influence multiple components of the carcinogenesis pathway, from initiation to progression.

In the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP), a study that was sponsored by Pfizer, the effectiveness of celecoxib (400 mg qd) in reducing the incidence of sporadic colorectal adenomas was evaluated. It recruited 1561 patients

from 107 sites in 32 countries. Patients were split into a 3:2 ratio of celecoxib (933) and placebo (628) and stratified for baseline aspirin use (17%). Of the total patients, 89% and 79% underwent a colonoscopy with or without removal of polyps at one year and three year respectively. Celecoxib reduced adenoma recurrence by third after one and three years (p < 0.001). The incidence of advanced adenoma (> 1 cm, tubulovillous or villous histology, high grade dysplasia, or invasive cancer) was reduced by 51%.

In the second study that was supported by the NCI, Adenoma Prevention with Celecoxib (APC) trail enrolled 2035 patients from 110 sites in the USA, UK, Canada and Australia. Patients were randomized to receive placebo (679), celecoxib 200 (586) or 400 (671) mg bid. A follow-up colonoscopy was conducted in 89% and 76% of the participants after one and three years respectively. In patients taking celecoxib polyp recurrence was reduced by 33% and 45% for patients taking 400 or 800 mg of the drug (p < 0.0001). The relative risk of advanced adenomas was even more drastically reduced 57% and 66% for patients taking the two dosages (p < 0.0001).

In a third study, run by Merck, for rofecoxib in the Adenomatous Polyp Prevention on Vioxx (APPROVe), rofecoxib, 25 mg qd, had been evaluated in comparison to placebo. 2547 from 110 sites were recruited. A 25% reduction in polyp recurrence was seen after one and three year.

However, all three studies were terminated earlier than planned due to substantial concern of increased in cardiovascular (CVS) toxicity. The CVS toxicity seen in the APPROVe trial caused Merck to withdraw rofecoxib from the market. In the APC trial, the CVS toxicity increased from 1.0% (n = 7/679) for placebo to 2.5% (n = 16/685) and 3.4% for celecoxib (200 mg bid and 400 mg bid, respectively) (p < 0.01). The proportion of all patients experiencing CVS toxicity in the PreSAP trial increased from 1.9% (n = 12/628) for placebo to 2.5% (n = 23/933) for celecoxib (400 mg qd) (p = NS).
On the other hand the gastrointestinal toxicity of celecoxib in the PreSAP and APC trials was recently adjudicated. There was no significantly difference between the drug and placebo for the entire 3 year duration of the study. Surprisingly, low dose aspirin (< 100 mg/day) was associated with significantly increase GI complication rate (HR 2.93).

The drug are still effective (in reducing adenoma recurrence and in particular advanced adenomas) and toxic (CVS toxicity), up to one (APPROVE) and two (APC and PreSAP) years after the drug was stopped. Interestingly, a rebound effect is seen in those who had received celecoxib and rofecoxib, implying that the drug inhibit the growth of adenomas, especially advanced adenomas, but it does not eliminate them.

In the intriguing jigsaw puzzle of cancer prevention, we now have a definite positive answer for the basic question "if", but several other parts of the equation (proper patient selection, ultimate drug, optimal dosage and duration, best screening modality) are still missing.

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Chronic inflammation and genetic polymorphisms

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Chronic inflammation very commonly accompanies gastrointestinal mucosal sites at increased risk for cancer, such as in inflammatory bowel disease, chronic gastritis caused by H. pylori infection, and reflux-induced esophagitis. What is not well understood is why some patients have more inflammation than others, and why only some individuals with chronic inflammation develop cancer. Current evidence suggests that differential degrees of cancer risk are not associated with highly-penetrant, single gene mutations. Minor genetic polymorphisms appear to be more important in mediating the inflammatory response, and the risk of cancer. One can consider two types of single nucleotide polymorphisms (SNPs) to understand the interactions among infection, inflammation and carcinogenesis. There are SNPs that mediate the degree of inflammation that occurs in response to an antigenic challenge, and these would include the NOD/CARD susceptibility loci, variations in the IL10, IL1B, IL23R, IL12B, JAK2, and STAT3 loci, SNPs in the toll-like receptors, and variations in the autophagy gene ATG16L1, to name just a few. There are also genetic variants that mediate differential risks for developing cancer in the context of chronically inflamed mucosa. One example is the interaction among the Cox-2 genes, aspirin use, and colorectal adenoma recurrence. Another example of interactivity is the role of a polymorphism in an intron of the ornithine decarboxylase gene that modifies binding by the transcription factor MYC, which mediates a 10-fold difference in polyp recurrence, but only among subjects taking aspirin. There are many others that will be discussed.

At present, the problem is the large number of genetic polymorphisms with a relatively modest individual effect, but which interact with specific environmental exposures. The challenge is to integrate a very large number of SNPs that appear to be important in mediating the inflammatory response with each other, and to understand the roles of environmental exposures. This represents an opportunity for informatics science to permit us to personalize our approach to chronic inflammatory diseases of the gut, and identify those at greatest risk for cancer.

Session II

Liver malignancies

Chronic hepatitis – Risk factor for hepatic carcinoma

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Hepatocellular carcinoma (HCC) is a major global health problem. It accounts for 80% to 90% of all liver cancers. HCC occurs more often in men than women and mostly in people 50 to 60 years old. The disease is more common in parts of sub Saharan Africa and Asia than in North and South America and Europe. Nevertheless its incidence has doubled in the past four decades in some Western countries. Worldwide, liver carcinoma is the fifth most common cancer and is the third most common cause of cancer mortality (behind only lung and colorectal cancer) with approximately 550,000 annual deaths. Unlike most of the other malignancies, HCC almost entirely develops in the context of inflammation and organ injury and is related to cirrhosis in about 85% of the cases.

Among underlying etiologies of liver cirrhosis, most frequent are viral infection and toxic substances, mostly alcohol. The evolution of HCC from cirrhosis is complex and multifaceted, involving both host genetic and environmental factors. The main HCC risk factor in Eastern Asia and Africa is hepatitis B virus (HBV) infection and it has been shown, that aflatoxin exposure has a synergistic effect with HBV infection. Aflatoxins are cancer-causing substances made by a type of plant mold and can contaminate wheat, peanuts, rice, corn and soybeans. Hepatitis C virus (HCV) infection is the main risk factor in Western countries. Various other cancer-causing substances are associated with primary liver cancer e.g. certain herbicides or such chemicals as vinyl chloride and arsenic. Men are more likely to get hepatocellular cancer than women, the question is if sex itself plays role or if it is caused by other independent factors like e.g. smoking, especially with abuse of alcohol or anabolic steroids, male hormones used by athletes to increase muscle, which can slightly increase liver cancer risk with long-term use. Hereditary hemochromatosis is not very frequent cause of liver cirrhosis, but these patients are in higher risk of HCC comparing with other etiology of cirrhosis.

HBV is a small, partially double-stranded DNA virus of the hepadnavirus family. The way it causes a tumor is complex; but integration into host cell DNA occurs at an early stage of cell infection. The expression of the viral HBx protein and the LHBs envelope protein alter control of host cell DNA transcription leading to cell proliferation (thus, these can be termed HBV oncogenes). HCV is a single-stranded RNA virus of the flavivirus family. It does not integrate into the host cell genome as it has no DNA provirus form. In HCV-infected cells, a protein called NS5A has been found to bind to p53 (among many other cellular proteins). NS5A is a phosphorylated non-structural protein that displays a multitude of activities related to enhancement of viral pathogenesis.

Initiation of HCC by HBV seems to occur in the early years of life since most patients have experienced a childhood HBV infection. In contrast, HCV-induced HCC often arises after an adult infection. Although HBV integrates into the host cell genome, whereas HCV does not, carcinogenesis induced by both viruses may be similar, not

only because it occurs in the liver. Mutations in p53 are common in both HBV- and HCV-induced HCC and even when there is no p53 mutation, normal p53 seems to binds to viral proteins.

Iron stores (what is important mostly in hereditary hemochromatisis) may stimulate hepatic fibrogenesis, either by leading to oxygen free radical injury and/or by inducing the production of profibrogenic cytokines such as transforming growth factor β (TGF-β). The generation of reactive oxygen species may directly lead to DNA damage and mutagenesis, and increased lipid peroxidation. As a result, stellate cells within the space of Disse become activated, leading to progressive collagen deposition overtime. Subsequently, hepatocyte proliferation is present with increased DNA synthesis. Conceptually, DNA damage and loss of tumor suppressor gene function through mutagenesis may lead to neoplastic transformation over time. This process is likely enhanced by the other before mentioned hepatotoxic factors (e.g. HBV, HCV).
Hepatic iron overload can play role even in patients with HCV, as it was observed in 30% of patients with hepatitis C, especially males.

Carcinogenesis of hepatocytes is a multi-factor, multistep and complex process and has many characteristics, such as fast infiltrative growth, metastasis in early stage, high malignancy, and poor therapeutic efficacy. Lesions range from liver cirrhosis to dysplastic nodules, but the underlying mechanisms are not fully understood.

Molecular pathogenesis is not clear. Genetic aberrations are frequent and can range from point mutations in individual genes to the gain or loss of chromosomal arms (e.g. chromosomal losses on 1p36.1, 4q21-25, 4q34-35.1, 8p23.3b-11.1, 13q14.1-14.3, 16p13.3, 16q22.1-24.3b, 17p13.3-13.1 and 17p13.3-11 or gains on 1q21-44f, 2q21.2, 2q34, 3q11.2, 5p14.2, 5q13.2-14, 7p22, 7p14.2, 7q21.1, 7q22.3, 7q34, 8q12-24.3 and 17q23). There is a lot of genes whose expression is dysregulated or where point mutations were described, what can change many functions: proliferation and differentiation, angiogenesis, metastasis, cell cycle or important function of growth factors and receptors in the beginning (e.g. dysregulation of epidermal growth factor receptor [EGFR] and insulin-like growth factor [IGF] family or overexpression of hepatocyte grow factor [HGF]; transforming growth factor α [TGF α] contributes to hepatocarcinogenesis via autocrine or paracrine mechanisms and can promote neoangiogenesis).

Les than 40% of patients are at present eligible for potential curative (surgical) treatment at the time if diagnosis. Systemic therapies do not have significant efficacy, so it is hoped, that clarifying the genomics and signaling pathways implicated in hepatocarcinogenesis can help with finding new therapeutic targets.

Biliary tract cancer – Pathogenesis and risk factors

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The group of biliary tract cancers comprises the intrahepatic cholangiocarcinoma, the biliary tree cancer and the gallbladder cancer. Taken together about 25,000–30,000 new diseases per year have been counted in the United States of America. This number is higher than that of oesophageal cancer or gastric cancer new cases. Nevertheless this tumor is considered as an "orphan tumor" by many cancer societies (including the German Cancer Society) and by the pharmaceutical industry as well.

Intrahepatic cholangiocarcinoma arises most frequently in cirrhotic livers. Adenocarcinomas in non-cirrhotic livers have been however found and not seldom immunhistological studies diagnose than cholangiocarcinomas. Caroli syndrom hepatitis viruses, alcohol consumption, NAFLD and especially primary sclerosing cholangitis are well recognized risk factor for intrahepatic cholangiocarcinoma.

Chronic inflammation seems to be the main pathomechanism of carcinoma development in the extrahepatic biliary tree. The predisposing conditions can be congenital or acquired. Choledochocystes can predispose to cancer development and. Biliary papillomatosis represents an seldom precancerosis.

Primary sclerosing cholangitis is associated with a significant risk of developing cholangiocarcinoma of the extrahepatic bile ducts as it is the parasitic infection of biliary tree in Thailand or China. It is still a continuous matter of debate whether cholecystolithiasis can be considered a risk factor for development of gallbladder cancer.

Recently smoking and diabetes have been associated with an increased risk of developing cholangiocarcinoma.
Thorotrast, Asbest (Asbestos), nitrosamine, methyldopa, dioxin, polychlorite Biphenyls are also considered to be risk factor for induction of CCC. Prevention strategies should be developed to prevent both intrahepatic and extrahepatic biliary cancer.

Endoscopic therapy of biliary tract malignancies

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Biliary tract malignancies include cancers arising in the gallbladder, bile ducts and ampulla of Vater as well as strictures caused by extrinsic compression, usually from pancreatic cancer and metastatic disease. Their common manifestation is biliary obstruction. Besides ampullary cancers, in majority of patients these tumors present at advanced, unresectable stage. Thus the main goal of therapy is the paliative biliary decompression.

Since its advent in 1979 biliary stenting has become the treatment of choice for malignant obstruction. Biliary stents are made of plastic or metal. Plastic stents (PS), made of different polymers, are tubular devices of various shapes and diameters. Straight 10F stents are most frequently used. Self-expandable metal stents (SEMS), made of steel or special alloys, reach the diameter of 30F and achieve longer patency times. The various SEMS models differ in shape, mesh cell size, flexibility, expansion force, mechanism of release, and the presence of coating.

Biliary stenting does not prolong the life but improves its quality. Successful biliary stenting can be achieved in more than 80% of patients. The results of stenting are comparable to that of surgical bypass, with significantly lower morbidity and mortality. Success rate of biliary stenting depends on the level of obstruction – the lower the obstruction level, the better the results. The treatment of hilar strictures is the most challenging.

The use of SEMS, in comparison to PS, increases the patency time at the expense of increased costs of the device. The median patency time of PS used for malignant obstruction is between 2 and 5 months, whereas that of SEMS is between 4 and 9 months. However, PS are around 25 times cheaper than SEMS. The use of SEMS is then cost-effective in patients with predicted survival of at least 4 months after stent insertion. There are no significant differences in patency time between various types of metal stents. Similarly to PS, larger diameter (30F) SEMS demonstrate longer patency times.

The role of preoperative drainage is a matter of controversy, but it seems not to influence the overall morbidity and mortality. Preoperative stenting is appropriate in patients undergoing neoadjuvant chemoradiation, but it should be done only after completion of staging procedure.

When access to obstructed biliary tree cannot be achieved on ERCP, EUS-guided cholangiography can provide an alternative. Endoscopic resection of ampullary tumors and additional techniques like photodynamic therapy or intraluminal brachytherapy complete the options of endoscopic therapy for biliary tract malignancies.

Session III

Gastric cancer

Epidemiology of pancreatic cancer

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Ductal adenocarcinoma of the pancreas has an incidence of approximately 10 per 100,000 population per year. This number pertains to Europe, North America and parts of South America (Argentina). Men are more often afflicted than women (female:male ratio of about 1:1.5, though reports vary). There has been a very small but steady increase in the incidence over the last 50 years, arriving at the quoted current number. The very much improved diagnostic possibilities, particularly imaging techniques, may account for some of this increase. Unfortunately, numbers for incidence and mortality are still practically identical for this cancer. The peak of incidence is between 60 and 80 years of age. In absolute numbers, in small countries like Austria (pop. 8 million), 1200 patients are diagnosed every year. In Germany, 8000 and in the United States, 30,000 cases are diagnosed annually. Pancreatic cancer below the age of 40 is extremely rare (2 cases per million per year) but among 80-year-olds, the incidence is about 200 new cases per 100,000 population per year. In men, carcinoma of the pancreas is the fourth most common cause of cancer death after lung, prostate and colorectal cancer. In women, it is the fifth most common cause of cancer death. The highest incidence with 20 per 100,000 per year is found in African-American males, while the lowest incidence, of 1 per 100,000 per year, is found in India, Singapore and Kuwait.

Molecular pathogenesis of H. pylori infection – The role of bacterial virulence factors

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Helicobacter pylori is one of the most common pathogens affecting humanity, infecting approximately 50% of the world's population. Of those infected many will develop asymptomatic gastritis, but 10% develop gastric or duodenal ulcers. The clinical outcome of the infection may involve a combination of bacterial factors, host factors as well as environmental factors.

In the process of development of gastritis, ulceration and cancers several cellular and molecular steps follow each other.

Adhesion, cytotoxicity, epithelial cell turnover changes, inflammation, regeneration or pathological alteration towards erosions, ulceration or cancer can be observed on the cellular level.

On the molecular level the first step of H. pylori invasion is the development of resistance to gastric acid. In this process the urease production is an essential step. Urease is a cytoplasmic enzyme that can be detected in minor volume also on the surface of H. pylori. Urease is serving also as an adhesin to the CD74 molecule of the epithelial cells. In addition to urease H. pylori posses other ammonia-producing enzymes, including two aliphatic amidases: AmiE, AmiF.

Chronic colonization of the mucosa is likely to be essential to the maintainance of a persistant reservoir of bacteria and subsequent cellular attachment and development of pathological alterations. Colonization is characterised by active movement of the H. pylori through the mucus covered epithelial surface. The colonization of H. pylori matches the expression of MUC5AC of the epithelial cells. The bacterial adhesin molecules include BabA, SapA/B, HpAA, UreB, UreA, AlpA/B and HopZ proteins. The adhesin receptors include the Lewis N blood group antigen, Sialyl Lewis X, Sialyl Lewis X, Cd74, DAF, phospholipids, TFF1 and heparan sulfate.

At the interaction of H. pylori with epithelial cells some effectors molecules start changing the functions of the epithelial cells after getting injected, penetrated into the gastric epithelial cells (GEC). These factors include cagA, vacAa, OipA, DupA and NAP.

cagA is part of the so called pathogenetic island (PAI). The cagPAI encodes the components of a type IV secretion system (T4SS) which has been shown to date to selectively transport two effector molecules the cagA and peptidoglycan into the host cells.

The intracytoplasmic NOD1 and extra- and intracytoplasmic toll-like receptors respond to the infection, leading to a cascade effect involving NF-κB activation, resulting in the production of inflammatory mediators such as IL-8. Phosphorylated cagA can interact with Src kinase activity. vacA exerts vacuolating cytotoxic effect in gastric cell lines and forms anion-conductive channels. OipA factor may be linked to increased bacterial adherence and colonization. DupA is associated with ulcer development.

Much of the current research on H. pylori is performed using in vitro systems that are not identical with in vivo conditions. Although several virulance factors have been described for H. pylori, a major drawback in determining their association with

specific disease is the fact that many strains isolated from asymptomatic patients also express them. Host and environmental factors must contribute to the development to their effects significantly and time, age dependent way.

H. pylori infection and gastric carcinogenesis and the potential of prevention

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The most threatful complication of H. pylori infection is gastric cancer. Gastric cancer occurs usually in advanced age with peak in the 6th decade and at the time of clinical manifestation the disease is in most cases (~ 85%) not curable. In the absence of premonitoring clinical symptoms prevention strategies offer the best chance. Testing for H. pylori and to treating with a positive result in a population of dyspeptic patients is a valid management strategy. However this strategy does not permit to prevent gastric cancer in the majority of patients as many of them never had dyspeptic symptoms before gastric cancer becomes apparent. Screen and treat in the general population would therefore be the strategy to aim for. However limitations of the current therapy option make it difficult to prescribe H. pylori indications for asymptomatic persons with the sole scope for prevention of gastric cancer. Moreover such a strategy would incur in a huge burden of expenses and find reluctance for being accepted by health regulatory authorities, even more so as the benefit would only be noticed a decade or more ahead.
The best approach and ready for application is test and treat complemented by a search and treat strategy in subsets of patients at risk.

Epidemiological data indicate approximately 70% of distal gastric cancers to be attributable to H. pylori. The lines of evidence for H. pylori as the most important risk factor in gastric cancer include the biological plausibility and the beneficial effect of H. pylori eradication on the progression from gastritis to gastric cancer. Experimental investigations that include animal models and numerous studies on human gastric tissues and cells complete the strong support for a causal role of H. pylori in gastric carcinogenesis.

Intensive current research aims at identifying the subset of individuals with H. pylori infection that eventually will develop the malignant disease. At present, there are few predictors for an increased risk of gastric cancer development among infected subjects. Attention has centred on microbial and host factors, which are both essential determinants for the clinical outcome of H. pylori infection. Among microbial virulence factors the CagA, pathogenicity island and defined allele types of the vacuolizing cytotoxin (VacA) are so far the best characterized.

Among host genetic factors functional polymorphisms of various genes related to the production of inflammatory molecules are the best studied contributors for gastric cancer development. Functional polymorphisms in the interleukin-1 beta (IL-1B-511/ -31), tumor necrosis factor alpha (TNF-A-308) genes and others significantly increase the risk of non-cardia gastric cancer.
The risk appears to be highest if both, host factors and bacterial at risk are simultaneously presend. The increased risk applies equally to the intestinal and diffuse type of gastric adenocarcinoma. The environmental plays a additional role but is less important than previously believed.

Future studies have to focus on better definition of subjects at risk, identify the point of no return in the pathway of gastric carcinogenesis despite H. pylori eradication and development of regional strategies for gastric cancer prevention.

Multimodal therapy of gastric cancer

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Introduction: Adenocarcinoma of the stomach is the second most common cancer worldwide. In 2001 gastric cancer affected 850,000 people. Tremendous geographic variations do exist in incidence of this disease – with highest death rates recorded in Chile, Japan and South America . The 5-years survival rates after curative surgical resection are ranging from 60–90% in stage I, from 30 to 50% in stage II and from 10–25% for patients in stage III of this disease.

Therapy

Surgical treatment is the only therapeutic modality with potentially curative effect.

Early gastric cancer (EGC) is limited to mucosa or submucosa regardless to lymph node involvement with 90% 5 years and 85% 10 years survival rates . In mucosal type (mEGC) nodal involvement is present in 3–5%, but in submucosal type (sEGC) lymph node metastatic spreading could be observed already in 16–21%. Usual endoscopic treatment for mEGC is endoscopic mucosal resection (EMR) when criterias of well differentiated, elevated (or flat) lesion with size up to 25 mm are fulfilled. Otherwise limited surgical approach (laparoscopic wedge resection including) with no need of D1 dissection in mEGC is performed. On the other side in sEGC surgical resection from limited one up to total gastrectomy combined with D2 dissection is indicated.

In advanced gastric cancer (AGC) with surgical approach – there are arising 3 main questions: 1. type of resection (total versus subtotal) 2. extent of lymph node dissection and 3. indication for splenectomy.

1. R0 resection – the ultimate goal for surgeon, is achieved by preserving 5 cm distance resection margins from primary tumor.

Randomized trials comparing subtotal with total gastrectomy for distal gastric cancer revealed similar morbidity, mortality and 5-years survival rates. On the other site total gastrectomy is prefered to subtotal in proximal gastric cancers.

2. Randomized trials compared D1 (perigastric lymph nodes) with D2 (hepatic, celiac, splenic and splenic hilar lymph nodes as well) – lymphadenectomy in patients treated with curative intention. Postoperative morbidity (43% versus 25%) and mortality (10% versus 4%) were higher in D2 group. Despite these negative results – D2 dissection (with pancreas and spleen preserving D2 lymphadenectomy) continue to be recommended by the National Comprehensive Cancer Network over D1 dissection.

3. Indication for splenectomy is tumor overgrowth to splenic hilus, and according Japanese authors also 11 and 12 group lymph nodal involvement. Splenectomy associated with higher morbidity and mortality.

Complications after surgery include postoperative bleeding, dehiscence of anastomosis , abscess formation and dehiscence or angling of duodenal stump.

In advanced stage IV gastric cancer, which has spread to distant organs, surgery is indicated in order to stop the bleeding or shrink the tumor. Endoluminal laser therapy or stent placement is performed to maintain oral nutrition.

Chemotherapy is indicated as a treatment of choice in disseminated stage of disease, when surgery and radiotherapy are performed only in palliative intention.

Many trials have been performed with adjuvant chemoradiotherapy ranging from stages I B up to III A stage. Using adjuvant and neoadjuvant chemoradiotherapy numerous trials were performed in stage III B and as well in stage IV (in this stage with palliative chemotherapic intention as well). Various chemotherapeutic agents including antimetabolits, antibiotics, taxans, platinum salts, and camptotecans are widely being used. According to metaanalysis studies combined chemotherapy seems to be superior compared to monotherapy. Combination of 5-FU, cis-platinum and antracyclins is associated with longer survival rate. Incorporation of new chemotherapeutic agents like taxans (docetaxel, paclitaxel) and irrinotekan as well, has lead to improved response in II phase of several trials. Perioperative chemotherapy or adjuvant chemoradiotherapy are recommended for inadequate operated patients, for patients operated with less than D1 dissection and for patients with high risk of relapsing (i.e. stage T3,T4 N1 M0). Untill now, there has been no consesus achiewed for patients with stage pT2N0M0, where individual approach is recommended. From new chemotherapeutic agents bevacizumab (a monoclonal antibody against vascular endothelial growth factor – VEGF) is currently being evaluated in advanced gastric cancer. Significant negative prognostic factor for gastric cancer means the overexpression of human epidermal growth factor receptor 2 – HER 2. International trial using this monoclonal antibody – trastuzumab is currently being tested in these HER 2 positive patients.

Radiotherapy as adjuvant locoregional treatment modality is indicated in combination with chemotherapy in above mentioned indications. Adjuvant radiotherapy as a monotherapy is practically not used.

Prognostic features
Survival rate in resectable gastric cancer is influenced mainly by the depth of invasion through the gastric wall and by the presence or absence of regional lymph node involvement. Positive margins (R1 or R2) in resected patients are associated with very poor prognosis. In advanced gastric cancers the effect of new chemotherapeutic monoclonal antibodies agents is currently being evaluated.

Session IV

Colorectal cancer

IBD as a risk factor for colorectal cancer

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Patients with long term inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's colonic disease (CD) have an increased risk of colorectal carcinoma (CRC). Duration of disease is recognized to be of the most important risk factor for development of CRC in patients with IBD. Eaden's the meta-analysis has shown that the risk for CRC in UC patients is 2% at 10 years, 8% at 20 years, and 18% at 30 years of disease. Now is accepted that the risk of colorectal cancer is equivalent in both (UC and CD) conditions. Extent of disease in another major risk factor. Most cancers arise in patients with extensive disease, which is generally defined as extension of inflammation beyond the hepatic flexure. It was demonstrated no increased risk for patients with UC included proctitis and proctosigmoiditis. The patients with left-sided colitis are an intermediate risk of CRC. The development of cancer in patients with left-sided colitis is not as frequent as in patients with pancolitis during the first 2 decades of disease, but the incidence of CRC in these 2 groups is equal by the fourth decade of disease. Recent data from the case control studies suggested, that greater degrees of colonoscopic or histologically active inflammation are associated with an increased risk of CRC. Recently it has been proved that shortened tubular colon, colonic stricture and postinflammatory polyps which are a results of ongoing inflammation should be considered strong risk factors for cancer. This findings require intensive colonoscopic surveillance. Primary sclerosing cholangitis (PSC) in patients with UC is associated with substantial risk of CRC. The recent analysis proved 4-fold increased risk of colorectal neoplasia in patients with PSC and UC, compared to patients with UC alone. Patients with IBD and a first-degree relative diagnosed with CRC before the age of 50 years are also an higher risk (RR 9.2; 95% CI: 3.7–23) of CRC. Is recommended that IBD patients with risk of CRC should undergo a screening colonoscopy with multiple biopsies thorough the colon to assess the true microsopic extent of disease. Screening colonoscopy should be performed in patients with UC to rule out colonic neoplasia 8–10 years after onset of symptoms. The interval between surveillance examinations is dependent on each individual's personal risk factors. In patients with a previous history of PSC, ongoing active inflammation, previous history of dysplasia or strictures, and strong family history of bowel cancer, annual surveillance is recommended. An intermediate cohort includes patients with postinflammatory polyps and a family history of bowel cancer later in life, for which surveillance examinations every 3 years is recommended. Patients with quiescent disease and no other risk factors for surveillance every 5 years is recommended. The British Society of Gastroenterology guidelines recommend chromoendoscopy and targeted biopsies as the prefered endoscopic method of surveillance. Unfortunately, in most countries is still recommended 2 to 4 random biopsies from every 10 cm of colon should be taken. Colectomy is recommended for patients with flat high grade dysplasia (HGD) which was confirmed by expert gastrointestinal pathologist. In patients with biopsy specimen considered indefinite for dysplasia, guidelines suggest colonoscopy between 3 to 12 months. Multifocal low grade dysplasia (LGD) is a stronger indication for colectomy. The optimal surveillance interval for patients with flat LGD is unknown, but 3 to 6 moths is

often recommended. Chemopreventive agents should be used to minimalize the risk of devoloping dysplasia or CRC in IBD patients. It has been shown a preventive effect of mesalazine for CRC (OR 0.51; 95% CI: 0.37–0.69) and for CRC plus dysplasia respectively. The benefit occured with regular use or use of at least 1.2 g/day of mesalazine equivalents. Most studies have noted that sulfasalazine appears to have less of an effect than mesalazine. A retrospective trial in patients with PSC and UC demonstrated that ursodeoxycholic acid (UDCA) was strongly associated with decreased incidence of colonic dysplasia. In prospective study of UDCA therapy was also associated with a significant reduction in the development of dysplasia and cancer. Little is know about whether UDCA might be chemopreventive for patients with UC who do not have PSC.

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The use of molecular markers in diagnosis of colorectal cancer screening

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Colorectal cancer (CRC) is among the most prevalent cancers and despite remarkable advances in detection and treatment of the illness, even in highly industrialized countries, more than a third of patients diagnosed with CRC ultimately succumb to the neoplastic lesions, often due to metastases. In stages I and II, where the tumor remains within the colon wall, surgical resection of the primary tumor usually suffices to cure the patient. In stage III, resection and adjuvant therapy are often effective, whereas in stage IV, where the tumor metastasized to distant lymph nodes and organs, therapy is rarely successful. Therefore, early detection of CRC is of paramount importance and the key to ultimately cure the vast majority of patients.

On the molecular level, chromosomal instability due to loss or inactivation of tumor suppressor proteins (e.g. APC, p53, SMAD4), DNA mismatch repair defects (e.g. loss of MLH1, MSH2), epigenetic silencing due to aberrant methylation of promoters (e.g. from MLH1), defects in base excision repair (e.g. MYH), and activation of oncogenic pathways (e.g. K-RAS, BRAF) are major triggers for CRC development. Consequently, additionally to the testing for fecal occult blood, assays for the detection of CRC-specific mutations and aberrant promoter methylation of fecal DNA have been established. Moreover, assays for profiling DNA, RNA, or proteins in the plasma to detect CRC in early stages, are the focus of intense research. The broad implementation of screens for CRC with high sensitivity and specificity should strongly increase the survival rate of cancer patients.

Advanced colonoscopic imaging

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Advanced colonoscopic imaging refers to the use of techniques such as high definition white light, standard white light with chromoendoscopy, virtual chromoendoscopy, magnification as well as endomicroscopy for the evaluation of the colon mucosa (1–3). When more than one of these methods is used we call it multimodal endoscopy (2–5). The main aims of advanced colonic imaging are to enhance the mucosal detail and to allow a detailed view of the submucosal capillary pattern, thus improve the detection of more pathological lesions (6, 7). All benign or malignant lesions that grow from or under the mucosa will "differentiate" themselves from its surroundings by virtue of various characteristics such as shape, size, and type of borders, color, shadows, absorbance or reflection of light, surface and subsurface pattern. Thus, by using advanced endoscopic imaging methods the aforementioned characteristics can be accentuated or discovered.

By scanning the mucosal surface the endoscopist is able to find dissimilarities of the mucosal integrity, detect growths, determine the shape of lesions, delineate their margins and investigate the submucosa. The gastrointestinal mucosa is not completely flat but has characteristic convolutions and openings or pits. Neoplastic and non-neoplastic growths develop into specific mucosal patterns which change the pit forms, which is called "pit pattern". Although early endoscopists had already noticed this aspect, it was Kudo et al who popularized the concept of classifying colon polyps by their pit pattern (7). He subdivided pits (pit patterns) into Roman numerals: round pits (I), stellar or papillary pits (II), small roundish or tubular pits (IIS, these are smaller than type I pits), large roundish or tubular pits (IIIL) (larger than type I pits), branch-like or gyrus-like pits (IV), and non-structured pits (V) (7). The pit pattern classification will be further discussed in the chromocolonoscopy section. But at this point we would like to emphasize that there are no prospective or outcome studies that have shown that this complex pit pattern classifications aids the endoscopist in the decision making process of colon polypectomy. The pit pattern classification has "good" sensitivity and "specificity for the characterization of colon polyps, ranging from 85–94% many experts, including us argue that a much higher sensitivity reaching 100% is mandatory when dealing with a neoplastic tissue such as an adenoma. If a colonoscopist is willing to leave a polyp behind based on a sensitivity of 90%, this would mean that 10% of unresected polyps are adenomas, and we are definitely not willing to risk this in clinical practice, especially if there are not outcome data to support the concept of leaving polyps behind based on pit pattern analysis. Furthermore, the Kudo classification may not be current anymore. We now know that many "hyperplastic" polyps are serrated adenomas (8). This aspect was not known when Kudo et al introduced his classification. Serrated adenomas have a classical hyperplastic appearance and even pathologists are still struggling to correctly diagnose these premalignat lesions (8). There is accumulating data that serrated adenomas are highly premalignant and develop into cancer (8). In summary, our experience has shown that although the pit pattern evaluation can aid

in the differentiation of many colon polyps, most experts would agree that any polyp larger than 10 mm should be resected, specifically it these are located in the proximal colon (13). In addition, we an others doubt on the rationale of leaving a polyp larger than 10 mm *in situ* solely based on the pit pattern (13).

Submucosal inspection (or submucosal surface analysis) is focused on visualizing the underlying vascular pattern of a given lesion (8, 9). The submucosal vascular pattern can be described based on the vascular pattern intensity and individual vessel characteristics (7). Thus, vessels are characterized endoscopically based on their amount, length, convolutions, elongations, tortuosity, looping and proliferative patterns (6). As angiogenesis is a major marker and promoter of malignancy, the endoscopically observed submucosal capillary network of a colon polyp can provide us with a clue regarding its neoplastic degree. Similar to what has happened to the "pit pattern" classification several experts have expanded on the submucosal vessel characteristics and baptized these with Roman numbers (6).

Therefore, advanced endoscopic imaging holds several promises for colonic diseases. Due to the improved ability to visualize the mucosa and submucosa, the endoscopist may be able to find or discover (i.e. *detection*) lesions or to better characterize (i.e. *differentiation*) them (5, 6).

Currently available advanced endoscopic methods include: high definition white light endoscopy, chromoendoscopy using methylene blue or indigo carmine, virtual chromoendoscopy using narrow band imaging (NBI) with colonoscope filtering devices or NBI using computerized image analysis (computerized virtual chromoendoscopy or CVC), autoimmune fluorescence imaging, magnification colonoscopy and confocal endomicroscopy (2, 4, 8, 10–12). Although many experts recommend using advanced image colonoscopy to *detect* lesions, current data is not strong enough to support this approach. This presentation describes current concepts and practice of advanced colonoscopic imaging.

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Rectal cancer highlights from the Czech National Cancer Registry

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Optimal therapy of rectal cancer can be selected only when basic diagnostic parameters are available and validated as prognostically significant. Despite published data the validity of basic stratification parameters should be reconfirmed also in local registries to ensure a proper evaluation of therapeutic outcomes in each country, region or center. Cancer surgery and surgical patology play basic diagnostic role.

Main required parameters can be abbreviated, especially for surgeons, as *No ReStInG* – exact examination of nodes (No), resection margins (Re), postoperative estimation of stage (St) and tumor grade, which is, besides of classical histopathologic grading, a broad area of further investigations on molecular predictors (InG – Investigation on Grade).

With this concept we assessed a prognostic values of these parameters for rectal cancer (ICD C20) in the database of the Czech National Cancer Registry, which includes more than 52,000 cases of rectal cancers reported since 1977. We selected *21,538 cases* from a ten-year period of 1996–2005 for analysis of median of survival (in months) in relation to basic prognostic parameters. Then we evaluated the impact of adjuvant therapies on survival rates.

As expected, *clinical stage* proved to be significant indicator of prognosis (MS stage I – 106, II – 54, st III – 32 and st IV – 7 months) as were the *depth of invasion* (MS T1 – 111,T2 – 92,T3 – 59, T4 – 21, all N0M0), *lymph node metastases* (MS of T2N0M0 – 92,T2N1M0 – 62, T3N0M0 – 59 and T3N1M0 – 38 months) and *resection margins* (MS of R0 – 69,R1 – 49, R2 – 19 months, all in stage II). However, histological grade showed some significance only for anaplastic G4 tumors (MS of G1 – 50, G2 – 58, G3 – 51, G4 – anaplastic – 20 months). Main histological types of rectal cancer were not prognostically useful (MS of tubular adenocarcinoma – 55, non-specified adenocarcinoma – 54, mucinous carcinoma – 53, cribriform carcinoma – 56).

Based on this local validation of prognostic factors the *impacts of adjuvant radiotherapy and chemotherapy* could be evaluated in properly stratified subgroups. Any radiotherapy, either preoperative or postoperative, improved outcomes in both, stage II (MS 69 vs. 38 months) and stage III (40 vs. 22), and also in T2N0M0 (112 vs. 76) and T3N0M0 (83 vs. 39) as subdivided stage II. *Preoperative radiotherapy* was superior to postoperative one in stage II (91 vs. 68) as well as in stage III (46 vs. 38). Standard a*djuvant chemotherapy* (based on FU/FA schemes only) improved median survival in both stages II (74 vs. 44) and III (44 vs. 21). Also *paliative chemotherapy* in advanced stage IV significantly improved median survival (15 vs. 3) in this retrospective study.

With an introduction of newer diagnostic parameters, surgical technigues and chemotherapeutic schedules, including biotherapy, the outcomes have to be systematically re-evaluated. But this will be possible only if local and regional databases are regularly updated, validated and used as essential measure for implementation of concept of evidence-based oncology, quality control and equity assurance.

Session V

Esophageal cancer

Etiology and risk factors for esophageal carcinoma

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Until 1990, gastric carcinoma was the most common cancer worldwide. Although there was a dramatic drop in the incidence of gastric carcinoma in most Western countries during the Twentieth century, it remains the second most common cause of death due to cancer in the world. The dramatic drop in gastric carcinoma incidence was mainly due to a strong decrease in the intestinal-type of non-cardia gastric cancer in which infection with *Helicobacter pylori* is thought to be the main etiologic factor. In contrast to non-cardia gastric carcinoma, gastric cardia and esophageal carcinoma were less common and occurred predominantly in high-risk groups, such as men with a history of smoking, alcohol use, or long-standing gastroesophageal reflux disease. However, trends toward increasing incidence rates were observed for esophageal and gastric cardia adenocarcinoma in Western countries, associated with trends toward stabilizing or declining incidence rates for esophageal squamous cell carcinoma, suggesting that these tumors might be associated with distinct risk factors. Another challenge related to this group of tumors is the dismal prognosis. The 5-year survival rate of esophageal cancer is often described to be around 5% although reports indicate that an increase to nearly 10% has been observed.

Squamous cell carcinoma has long been the most common histological form of cancer in the esophagus. For the last decade reports have shown a rising incidence of esophageal adenocarcinoma in most of the western world, although unchanged in Asia and South America. Cancer of the esophagus represented 0.8% of all new cases of cancer in for instance Sweden 2004 (male: 1.1% and female: 0.4%). Cancers of the cardia are almost always adenocarcinoma and represented 0.4% (male 0.6% and female 0.2%).

Methodological considerations:

The observed regional variations in the incidence rates of cardia and esophageal adenocarcinoma may be due in part to methodological problems. For instance are there difficulties in the classification of cancers arising at the gastroesophageal junction. Although a standardized set of diagnostic criteria and classification methods have been used in the different epidemiological studies, the implementation of these criteria can vary between regions and studies. In particular, the classifications of tumors near the gastroesophageal junction as either esophageal or gastric in origin might differ between registries or over time. Therefore, it is important to analyze combined rates, such as all adenocarcinoma of the gastroesophageal junction and all types of gastric and esophageal cancers.

Improvement in precision of histological diagnosis and improvement in diagnostic procedures (such as increased use of endoscopy) may have affected the incidence rates of adenocarcinoma of the esophagus as well. The rise in incidence of adenocarcinoma of the esophagus is often accompanied by a much greater fall in rates of tumors with 'unspecified morphology' and 'no morphology'. It is unknown which proportion of tumors coded in early years of the study period as 'unspecified morphology' or 'no morphology' are being coded as adenocarcinoma of the esophagus in later years of the study period.

Besides changes in histological verification of tumors of the esophagus and stomach over time, the improvement of precision of histological diagnosis and diagnostic has changed. Moreover the increase in incidence in adenocarcinomas of the esophagus and cardia might be explained by the introduction of a 'new' environmental risk factor in the aetiologically relevant period

In order to circumvent the potential problem of difficulties in distinguishing tumors arising in the lower third of the esophagus, the gastroesophageal junction and the gastric cardia and changes in classification or coding practice regarding these tumors in the study period, attempts have been made to combine adenocarcinomas of the esophagus and gastric cardia for analyses. Applying similar background information it has become clear that certain cancer registries used to classify adenocarcinomas of the lower esophagus as cardia tumors in the study period. Some cancer registries coded tumors to 151.0 in case of doubt about localization of an adenocarcinoma in the lower esophagus or cardia.

Therefore difference in incidence rates of adenocarcinoma in the esophagus and gastric cardia could partly be explained by misclassification. Reports show that there can be a significant mismatch between adenocarcinomas in the anatomic region, although the disagreement of classification seems to be present in both directions. Reasons for this mismatch are unknown but enhanced diagnostic tools, increasing awareness of the diseases and lack of consensus regarding anatomic classification could be factors contributing to a possible misclassification.

Epidemiological trends:

An increasing incidence trend of adenocarcinoma has been reported from Denmark and England and Wales, confirming previous observations in other studies of population-based cancer registries in the same countries. A recent Dutch study reported stable gastric cardia cancer mortality rates between 1969 and 1994 but nearly all other time-trend studies conducted in European countries, the US, Australia and New Zealand report an increase in incidence, either in adenocarcinomas of the esophagus or adenocarcinomas of the gastric cardia or a combination of two sites of the esophagus and cardia. Exceptions have been a study from Switzerland which reported a stable incidence of adenocarcinomas of the cardia during the period 1976–1987 in both men and women and a study in France (Côte d'Or and Calvados) which reported no significant change in incidence of adenocarcinomas of the esophagus during the period 1978–1987. Some studies reported an increase in incidence of adenocarcinomas of the esophagus or cardia being most predominant in males. On the other hand similar trends have been revealed in females but at a considerably different and lower rate.

The incidence of adenocarcinoma in the esophagus can be seen throughout many western countries. There are of course differences in the rate of increase between various countries with no increase at all in some parts of Europe whereas from U.S. the highest rates are reported.

The incidence of squamous cell carcinoma e.g. in Sweden is decreasing for men and is fairly stable for women, which concurs with reports from countries throughout Europe where the incidence have been reported to be relatively stable with a tendency among men for rates to decline where as for women it is stable and in some countries even increasing. Urban regions are also at larger risk of squamous cell carcinoma as described repeatedly.

Aspects on etiology.

The unfavorable trends for cardia and esophageal adenocarcinoma have been related to a number of risk factors that differ from those for esophageal squamous cell carcinoma. Overweight and obesity have been consistently related to esophageal adenocarcinoma but not to squamous cell carcinoma. Indeed, body mass index seems to be inversely related to the risk of esophageal squamous cell carcinoma. The influence of obesity on esophageal adenocarcinoma and gastric cardia adenocarcinoma may be related to higher incidence of gastroesophageal reflux in obese persons, since the risk of gastroesophageal reflux is strongly related to the risk for Barrett's esophagus. Tobacco smoking is a strong risk factor for esophageal squamous cell carcinoma, but is only a weak risk factor for esophageal adenocarcinoma. Alcohol drinking is a strong risk factor for esophageal squamous cell carcinoma but is not consistently related to esophageal adenocarcinoma. Alcohol drinking and tobacco smoking account for over 80% of esophageal squamous cell cancers in developed countries. In summary, putative risk factors for esophageal and cardia adenocarcinoma include gastroesophageal reflux, obesity, dietary factors, smoking, alcohol drinking, and inversely associated with gastric colonization with *H. pylori*.

The etiology of the continuous increase of adenocarcinoma of the esophagus has been the focus of many studies. Overweight, Barrett's esophagus, dysplasia and tobacco smoke are some reported risk factors as well as low socioeconomic status. Selenium, dietary fibre, fruits and vegetables and antioxidants are seen as protective factors. Male gender seems to be a risk factor for both types of tumors in the region, while infection with human papilloma virus (HPV) does not seem to play a major part in the development of esophageal cancers. Infection with *Helicobacter pylori* is, however, an interesting factor to this region of tumors as discussed in many reports. It has been suggested that infection with *H. pylori* is protective to adenocarcinoma but might be a risk factor for squamous cell carcinoma, although the role of *H. pylori* in the etiology of these cancers remain somewhat unclear. The anatomic region of these tumors is also of interest. Not only are there disparities in the classification of esophageal and cardia tumors, the adenocarcinomas of the distal esophagus, Siewert type I, and gastroesophageal junction, Siewert type II, show different epidemiological profiles. It is still unclear if this is one disease in two locations or two different diseases altogether.

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Oesophageal carcinogenesis

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Adenocarcinoma develops at the lower end of the oesophagus near to its junction with the stomach. The cancer arises against a background of progressive histological changes which are thought to be due to chronic mucosal damage induced by the reflux of gastric and duodenal juices. The exposure to refluxing acid, pepsin and bile produces inflammation, erosions and ulceration of the squamous oesophageal mucosa. Unlike the stomach, the oesophagus is not designed to withstand these substances. In response to this environmental challenge, the epithelium of the distal oesophagus undergoes metaplasia, changing from a multi-layer squamous epithelium to a single layer columnar epithelium referred to as Barrett's oesophagus. The phenotype of this columnar epithelium has a mosaic pattern with some areas resembling the gastric antrum, some small intestine and others colonic mucosa. This change in phenotype of the epithelium is thought to represent an adaptive change to its altered environment. Gastric and small intestinal epithelium are intrinsically more capable of withstanding the noxious effects of acid, pepsin and bile. Consistent with this adaptive response, patients who develop Barrett's oesophagus often notice an improvement in their reflux symptoms.

One problem with the oesophageal epithelium changing in response to its new environment produced by gastric reflux is that this new luminal environment is constantly changing. The intermittent nature of the reflux means that the luminal environment varies markedly with respect to its acidity (pH1–pH7), as well as its peptic activity, bile concentration and bacterial content. This varied and changing luminal environment is reflected in the phenotype of the Barrett's mucosa which in some areas resembles the stomach, others small intestine, others large intestine and many areas showing a mixed phenotype. The environment of the distal oesophagus induced by gastric reflux sends confusing signals to the epithelium producing a varied and confusing phenotype. The epithelium becomes hyperproliferative as it constantly tries to adapt to the constantly changing environment. This genetic instability is associated with increased risk of progression to dysplasia and neoplasia.

Consistent with the above environmental challenge, Barrett's mucosa usually shows evidence of chronic inflammation both histologically and with respect to its cytokine expression profile. Though Barrett's represents an adaptive response to the altered luminal environment, the inflammation indicates that the metaplastic epithelium is not ideally suited to the new environment. This is consistent with the environment constantly changing and thus making it impossible to express a phenotype which is perfectly suited to such a challenging environment.

Understanding the pathogenesis of oesophageal neoplasia reveals potential ways of preventing the progressive changes. Anti-inflammatory agents such as low dose Aspirin may be helpful and are under investigation. Preventing reflux by Proton Pump Inhibitor therapy or anti-reflux surgery is also likely to have a place. However, once Barrett's has developed, preventing progression will probably require stabilising the luminal environment by Proton Pump Inhibitor therapy plus or minus reflux

surgery and removing the Barrett's mucosa and allowing new mucosa to develop which is appropriate for the new environment. Simply preventing acid reflux once Barrett's has developed is unlikely to be sufficient as the Barrett's mucosa will not be appropriate for the restored normal distal oesophageal environment.

New diagnostic endoscopic approaches to esophageal cancer

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The prognosis of oesophageal neoplasia is dependent on the stage of the disease at the time of detection. Early lesions have an excellent prognosis in contrast to more advanced stages that usually have a dismal prognosis. Therefore, the early detection of these lesions is of the utmost importance. In recent years, several new techniques have been introduced to improve the endoscopic detection of early lesions. The most important improvement, in general, has been the introduction of high-resolution/high-definition endoscopy into daily clinical practice.

The value of superimposing techniques such as chromoendoscopy, narrow band imaging and computed virtual chromoendoscopy onto high-resolution/high-definition endoscopy will have to be further proven in randomized cross-over trials comparing these techniques with standard techniques. However, first data are available that these filter technologies enable new mucosal or vessel details to be seen, which can be used to increase the diagnostic yield of Barrett's associated neoplasias.

Important future adjuncts to white-light endoscopy serving as 'red-flag' techniques for the detection of early neoplasia may be broad field functional imaging techniques such as video autofluorescence endoscopy. Here false positive results compromise the clinical value. Thus autofluorescence has to be combined with other imaging modalities.

In addition, real-time histopathology during endoscopy has become possible with endocytoscopy and confocal endomicroscopy. Endomicroscopy enables for the first time in vivo histology during ongoing endoscopy. This leads to new diagnostic algorithms, because goblet and cancerous cells can be definitely identified.

The concept of smart biopsy is already achieved and the future will show how much we can reduce random biopsies in patients with esophageal cancer or precancerous conditions.

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Multimodal treatment of esophageal cancer

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Background: Locally advanced esophageal cancer remains to be a therapeutic challenge. Low rates of complete resection (CR) and limited survival even after CR including lymphadenectomy stimulated the development of multimodal approaches. Those comprise pre- and postoperative regimen of chemotherapy and/or radiotherapy.

Methods: The lecture provides an overview of scientific evidence regarding perioperative multimodal treatment for locally advanced esophageal cancer.

Results: Adjuvant chemotherapy or radiotherapy did not show survival improvement. According to recent metaanalyses neoadjuvant chemoradiotherapy is able to reduce tumor related mortality, the number needed to treat to prevent one death (NNT) is 7 to 10. However, only patients with complete or subtotal pathological response benefit (20–30%). On the other hand, preoperative radiochemotherapy enhances surgical morbidity and hospital mortality. The effect of neoadjuvant chemotherapy is less remarkable, NNT is 8 to 20. But neoadjuvant chemotherapy does not increase surgical risk. Non-responders to preoperative treatment tend to have worse outcome even compared with patients undergoing surgery alone.

Conclusion: Neoadjuvant treatment is able to enhance survival. Overall, radiochemotherapy seems to be more effective than neoadjuvant chemotherapy. As a disadvantage of radiochemotherapy, it is followed by a remarkably higher rate of postoperative complications. Unfortunately, up to now we are not able to anticipate, who will benefit from preoperative multimodal treatment. Thus, the majority of patients – the "non-responders" – undergoing preoperative radiochemotherapy is exposed to enhanced surgical risk without having any benefit from the multimodal approach. Hopefully predictive factors for response can be identified in the near future.

**State-of-the-art-lecture
Dr. Herbert Falk memorial lecture**

The advances in screening for gut malignancies

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In the foreseeable future, more people will die from tumors than from cardiovascular diseases, currently the number one killer. Tumors of the digestive tract are, as a group, by far the most common form of cancer. The prognosis for this type of cancer remains poor, because it develops no apparent symptoms in its early stages, and when it eventually does, it is often locally advanced, has already developed metastases and is generally difficult to treat. Reliable biomarkers for screening and early diagnosis have not yet been developed to the point of large-scale practical application, and no primary preventive strategies are known that would appear to guarantee success. Possibilities of highly active treatment for gastrointestinal carcinomas only exist in about 20% of all cases.

If we want to improve the outcome for patients with gastrointestinal cancers, we shall need to intensify our research into the early detection of easily treatable tumor lesions in the preliminary and early stages of the disease and into the screening of high-risk groups of people.

Suspicious lesions should be more often – and more effectively – evaluated in vivo, in the course of an endoscopic examination, and be subjected to minimally invasive forms of treatment. This is something that white light endoscopy has significantly failed to deliver. We must conduct research into the potential of chromoendoscopy, zoomendoscopy, narrow band imaging, auto-fluorescence endoscopy and various combinations of these techniques. It is already possible to perform optical biopsies with confocal laser microscopes, allowing the doctors to look into and underneath the gastrointestinal mucosa to detect indications for tumors at the blood vessels and to diagnose malignancies that have developed from chronic infections such as Barrett's Esophagus, sprue or ulcerative colitis. Endoscopic biopsies performed with either this method or with fluorescence endoscopy take up less time. The conventional white light endoscopy can only detect tumorous developments in the gastrointestinal tract at a fairly late stage. We shall need to strive to uncover and visualize tumor-specific biological processes in the early stages of the disease, using contrast agents that dock specifically to molecular target structures, proceeding non-invasively and at an early stage on the molecular level by applying newly developed fluorescence endoscopes. This innovative method of endoscopic early detection of tumors is already being subjected to experiments and trials in small and large animal models.

The screening of gastrointestinal cancers in the general population and the monitoring of people who are at specifically high risks of developing such cancers will be performed with the help of simple blood and urine samples which show changes on a molecular level that indicate the presence of gastrointestinal tumors (such as hypermethylation). The subsequent identification and localisation of the tumor will be the preserve of innovative endoscopy techniques.

Session VII

Pancreatic cancer

Chronic pancreatitis and pancreatic cancer

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Chronic pancreatitis (CP) is well recognized as a risk factor for the development of pancreatic cancer (PC). The mechanism may be similar to the increased risk of cancer due to chronic inflammation in other sites of the body. In the United States, more than 30,000 cases of PC are seen every year and it is the only cancer where the mortality rate almost approaches the incidence rate. The incidence and prevalence of CP in the United States are about 8 and 26.4 per 100,000 population respectively. The relationship between CP and PC can be discussed under the following headings.

Chronic inflammation and cancer:
Virchow described presence of inflammatory cells in cancer in 19th century. Subsequently, increased risk of cancer was noted in organs with chronic inflammation. Colorectal cancer in patients with inflammatory bowel disease is a good example of chronic inflammation leading to cancer in GI tract. Chronic inflammation damages the cells, which results in cytokine release and reactive oxidant stress. Later these cells during healing are exposed to growth factors, and inhibition of apoptosis. This abnormal microenvironment in chronic inflammation that promotes cancer is termed as "landscape theory". This leads to more DNA damage and proliferation, ultimately resulting in cancer.

Epidemiologic evidence of increased risk of PC in CP:
Lowenfels and colleagues reported a 4% cumulative risk of PC at 20 years in a cohort of 2015 patients with CP. The same risk was confirmed in patients with CP by later studies from Sweden, Italy, USA and other countries. Cigarette smoking was felt to increase the risk further while similar risk was noted in alcoholic and non-alcoholic CP. A similar increased risk of PC was also noted in tropical pancreatitis, a special type of CP. A study reporting 266 patients with tropical CP found a the risk of PC to be 8.3%. Higher risk of PC was also reported in cystic fibrosis-associated CP. Thus CP increases PC regardless of the etiology but the subgroup, hereditary pancreatitis-associated CP resulted in much higher risk of PC. EUROPAC study followed a large cohort of hereditary pancreatitis and found that 44% of those patients developed PC by age 70. However, in this subgroup smoking increased the risk of PC further when compared to non-smokers as also the duration of CP.

Mechanisms of Carcinogenesis in CP:
PC is the result of many factors operating in CP. Cytokines, chemokines, free oxygen radicals and growth factors are various mediators of chronic inflammation. These cause DNA breaks, genetic mutations in cells which include K ras mutation, p16 and DPC4 inactivation, p53 over-expression, and alteration of genes like BRCA2. These mutations cause defective DNA repair and apoptosis, eventually leading to cancer. NFκB, a a transcription factor, may control genes responsible for accelerating angiogenesis, inhibiting apoptosis and also stimulating NFκB thus creating a self-sustaining loop. This mechanism again promotes the landscaper defect conducive to

cancer formation. There is also evidence that COX-2, a known mediator of chronic inflammation, plays a role in carcinogenesis by cell proliferation, release of cytokines and inhibition of immune surveillance. Finally, there is also emerging evidence that systemic inflammatory response in established cancers (high CRP and low albumin) may be indicators of worse prognosis.

Thus, there is enough epidemiologic and pathogenetic evidence that CP can lead to PC. Also it may be difficult sometimes to distinguish between the two in clinical practice and also to diagnose PC in a patient known to have CP. There are currently no known screening protocols for early recognition of PC in CP. Future studies are highly needed for prevention and early recognition of PC in CP.

Is early diagnosis of pancreatic cancer fiction?

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Pancreatic cancer is one of the most fatal of all malignancies. The median survival after diagnosis is six months. The overall 5-years survival is less than 5 percent. Despite improvements in imaging and surgical techniques, survival statistics have hardly improved over the past decades. Resection offers the only chance for cure, but due to early vascular involvement and/or metastatic spread only a minority (10–20%) of symptomatic patients is eligible for surgery. Sadly, even after resection, the outcome in these patients is disappointingly low with a 5-year survival of only 10–30%. Consequently, to improve this dismal outlook it would be desirable to detect small asymptomatic early cancers or, more preferably precursor lesions, at the time when the disease is still at a curable stage. Well-defined pre-cursor lesions of pancreatic cancer include pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia (IPMN). Detection and resection of these lesions before they turn malignant might improve survival. Because of the relatively low incidence of the disease and the lack of accurate, inexpensive and non-invasive diagnostic test for detection, screening of the general population is not realistic. However, screening and surveillance might be feasible in a well-defined population of individuals at high-risk for this fatal disease. Individuals at high risk of pancreatic cancer (PC) are either (1) mutation-carriers of PC prone hereditary tumor-syndromes (e.g. p16-Leiden carriers, Peutz-Jegers syndrome, BRCA2) or (2) first-degree-relatives of patients with familial-PC (FPC). The current status of pancreatic cancer screening and surveillance in these high-risk individuals will be discussed in this lecture.

What's new in therapy of pancreatic cancer?

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Pancreatic cancer remains to be a dismal disease with a median survival after diagnosis of about 6 months. The title of the lecture is more promising in comparsion to reality. Diagnosis is still made rather late. Thus, only about 20% of all patients will have the chances of a R0-resection. Adjuvant chemotherapy after R0-resection is standard: gemcitabine seems to be superior to 5-FU or no therapy. Nevertheless only a few patients survive for at least 5 years after R0-resection and adjuvant chemotherapy. There are several factors which have positive influences on survival after pancreas resection: well differentiated tumor grade, low tumor size, no duodenal or major vessel invasion, no perineural invasion, negative lymph node status, resection margin negativity (R0) versus positivity (R1), high-volume vs. low-volume centres, presence of human equilibrative nucleoside transporter 1 in patients treated with gemcitabine, low pre-operative tumor marker CA 19-9, low bilirubin level. The role of socioeconomic status and ethnicity is unknown. The following factors seem to have no influences on survival after pancreas resection: age, blood loss and transfusion requirements following resection, location of tumor, type of resection.

Most patients need palliative treatment. Besides best supportive care including nutritional support, therapy of pain, and endoscopic treatment of jaundice, gemcitabine is standard in both locally advanced and/or metastatic disease. The addition of the tyrosine kinase inhibitor erlotinib prolongs median survival according to a randomized trial for only 2 weeks. Erlotinib has only beneficial effects in those patients who develop skin rash. None of the studied combinations of various chemotherapies, addition of various other inhibitors of tyrosine kinases, inhibition of vascular endothelial growth factor, intraoperative radiation etc. have really demonstrated any additional benefits. In table 1 the results of randomized clinical trials published as full articles within the last three years are shown. The only promising combination therapy in the palliative situation seems to be a combination therapy of gemcitabine together with capecitabine. However, further trials including more patients are still needed before one can recommend this combination. The potential benefits of a combination therapy of gemcitabine with oxaliplatin in those patients having an excellent Karnofsky index are still discussed controversially. Table 2 shows trials which aimed to improve the clinical outcome after R0-resection. Again, there are no "breakthroughs".

Table 1: Phase II or III trials published in full length as original articles: Chemotherapy in locally advanced and/or metastatic pancreatic cancer

Authors	Journal	Cancer state	N of pats	Chemotherapy	Survival (months)
Bernhard et al.	J Clin Oncol 2008; 26: 3695–3701	Locally advanced or metastatic	319	Randomized multicenter phase III Clinical benefit + quality of life Gemcitabine 1 g mg/m^2 30-min inf days 1, 8 every 3 w + capecitabine (650 mg/m^2 twice daily days 1–14) vs. gemcitabine alone weekly for 7 weeks, 1-week break, then weekly for 3 weeks every 4 weeks for 24 weeks or until progression	No difference in CBR or QOL between GemCap and Gem
Chauffert et al.	Ann Oncol 2008; 19: 1592–1599	Locally advanced	119	Phase III Chemoradiotherapy (60 Gy, 2 Gy/fraction; concomitant 5-fluorouracil infusion, 300 mg/m^2/day, days 1–5 for 6 weeks; cisplatin, 20 mg/m^2/day, days 1–5 during weeks 1 and 5) vs. gemcitabine (1 g/m^2 weekly for 7 weeks) Maintenance gemcitabine (1 g/m^2 weekly, 3/4 weeks) in both arms	Median survival 8.6 vs. 13 1-year survival 32% vs. 53%
Ciuleanu et al.	Eur J Cancer 2009; 45: 1589–1596	Metastatic	303	Randomised Phase III Glufosfamide vs. best supportive care (BSC) Previously treated with gemcitabine	18% increase in overall survival n.s. Median survival 105 (range 5–875) days glufosfamide vs. 84 (range 2+ to 761) BSC
Cunningham et al.	J Clin Oncol 2009; 27: 5513–5518	Locally advanced	533	Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine	GEM-CAP improved objective response rate + progression-free survival Trend towards improved survival
Eckhardt et al.	J Pain Symptom Manage 2009; 37: 135–143	Locally advanced	244	Double-blind, placebo-controlled Gemcitabine + tipifarnib vs. gemcitabine + placebo	Time to deterioration 69 vs. 91 days No difference
Karasawa et al.	Radiother Oncol 2008; 87: 326–330	Locally advanced		Placebo-controlled randomised Intraoperative radiotherapy Hypoxic cell sensitiser doranidazole	Short-term survival not different 3-year survival 23% vs. 0%

Kulke et al.	J Clin Oncol 2009; 27: 5506–5512	Metastatic	245	Randomized phase II A: gemcitabine 1 g/m^2 days 1, 8, 15 + cisplatin 50 mg/m^2 days 1, 15 B: gemcitabine 1 g/m^2, rate of 10 mg/m^2/min days 1, 8, 15 C: gemcitabine 1 g/m^2 + docetaxel 40 mg/m^2 days 1, 8 D: gemcitabine 1 g/m^2 + irinotecan 100 mg/m^2 days 1, 8	No difference 6.4–7.1
Poplin et al.	J Clin Oncol 2009; 27: 3778–3785	Locally advanced + metastatic	832	Phase III, randomized Gemcitabine + oxaliplatin vs. gemcitabine (fixed-dose rate infusion) vs. Gemcitabine (30-minute infusion)	median survival & 1-year survival: GEM: 4.9, 16% GEM FDR: 6.2, 21% GEMOX: 5.7, 21% 9.2: locally advanced vs. 5.4 metastatic disease
Spano et al.	Lancet 2008; 371: 2101–2108	Locally advanced and/or metastatic	69 vs. 34	Open-label randomised phase II Gemcitabine + axitinib (5 mg twice daily) (inhibitor of VEGF receptors 1,2,3) vs. gemcitabine alone	6.9 [95% CI: 5.3–10.1] vs. 5.6 [3.9–8.8]
Sultana et al.	BMC Cancer 2009; 9: 66	Locally advanced	19	Randomised Phase I/II radiolabelled anti-CEA (131-I) 9 i.v. vs. 10 i.a.	Median overall survival 5.2 No difference
Van Cutsem et al.	J Clin Oncol 2009; 27: 2231–2237	Metastatic	301	Phase III Gemcitabine(1 g/m^2/week), + erlotinib(100 mg/day) + bevacizumab (5 mg/kg every 2 weeks) vs. gem + erl + placebo	Median OS 7.1 vs. 6.0 ns improved PFS
Wasan et al.	Br J Cancer 2009; 101: 1162–1167		95	Gemcitabine plus axitinib vs. gemcitabine	Low vs. high Ca19-9 12.5 vs. 4.9 12.2 vs. 5.0 dBP > 90 mmHg: longer OS
Xinopoulos et al.	J BUON 2008; 13: 341–347	Locally advanced	49	Randomized controlled Gemcitabine vs. observation Previously treatment with covered metal stent due to jaundice	Median survival 21 vs. 22 weeks

Table 2: Adjuvant chemotherapy in pancreatic cancer

Authors	Journal	Number of patients	Chemotherapy	Survival (months)
Caprotti R et al.	Anticancer Res 2008; 28: 1951–1954	30	Randomized Radical surgery alone vs. preoperative immunotherapy IL-2 (12 MIU/day SC for 3 consecutive days) + surgery	Follow-up of 36 m free-from-progress. period + overall survival higher with IL-2
Farrell et al.	Gastroenterology 2009; 136:187–195	538	Gemcitabine vs. 5-5-FU	Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine: Longer overall and disease-free survival
Morak et al.	Ann Surg 2008; 248: 1031–1041	120	Prospective rand. controlled Adjuvant i.a. chemotherapy mitoxantrone, 5-FU, leucovorin, cisplatinum + radiotherapy 30 x 1.8 Gy vs. surgery alone	19 vs. 18 ns Less liver metastases
Regine et al.	JAMA 2008; 299: 1019–1026	230 vs. 221	Rand. controlled, phase III Fluorouracil (continuous infusion, 250 mg/m^2 per day vs. gemcitabine (30-minute infusion of 1 g/m^2 once per week) for 3 weeks prior to chemoradiation therapy and for 12 weeks after chemoradiation Chemoradiation with a continuous infusion of fluorouracil (250 mg/m^2 per day) same for all (50.4 Gy)	Median survival 20.5, 3-year survival 31% in gemcitabine group vs. 16.9, 22% in fluorouracil group ns
Ueno et al.	Br J Cancer 2009; 101: 908–915	118	Gemcitabine vs. surgery alone gemcitabine 1000 mg m^{-2} over 30 min on days 1, 8, 15, every 4 weeks, 3 cycles	Longer disease free survival 11.4 vs. 5.0 Median survival not different: 22.3 vs. 18.4
Yoshitomi et al.	Cancer 2008; 113: 2448–2456	100	Randomized phase II Uracil/tegafur + gemcitabine vs. gemcitabine alone	21.2 vs. 29.8

Adjuvant therapy of pancreatic cancer

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Background

Pancreatic cancer is one of the major causes of cancer death in Europe the USA and globally with a five year survival rate of less than 5%. The outlook for those patients who can undergo surgical resection is better. In specialised centres, resection rates of above 15% can be achieved. Although surgery cannot guarantee a cure, the five year survival does improve to around 10% following resection and increases to 20-30% with adjuvant chemotherapy.

Adjuvant chemoradiotherapy

There have been several randomised trials which have assessed adjuvant therapies in resected pancreatic cancer. The European Study Group for Pancreatic Cancer (ESPAC) 1 trial was the first adequately powered, randomised study to assess chemoradiotherapy (split course [total 50 Gy], concurrent with 5-fluorouracil [5-FU]) and chemotherapy (5-FU, 425 mg/m^2, d1-5 and folinic acid, 20 mg/m^2, d1-5, repeated monthly for six months) in resected pancreatic cancer. There was a survival benefit for adjuvant chemotherapy (5-FU/FA) but not for adjuvant chemoradiotherapy (40 Gy split course) in the final analysis of the 2 x 2 factorial group of 289 patients. The failure of adjuvant chemoradiotherapy to improve survival observed in the ESPAC-1 trial was also reflected in the results of the EORTC multicentre prospective randomised trial by Klinkenbijl et al. Overall survival after follow-up of 11.7 years reaffirmed that there was no difference in overall survival between the two arms (death rate ratio 0.91, 95% confidence interval [CI]: 0.68–1.23; p = 0.54). The Radiation Therapy Oncology Group Study 9704, a phase III trial, compared pre-and post-chemoradiation gemcitabine (at a dose of 1000 mg/m^2/day) to pre- and post-chemoradiation 5-FU (at a dose of 250 mg/m^2/day given as a continuous infusion). Overall 538 patients were recruited there was no difference in overall survival between the two arms (median survival 16.7 months for the 5-FU group versus 18.8 months for the gemcitabine group; p = 0.34). The case for adjuvant chemoradiotherapy with follow on chemotherapy remains to be proven and does not provide a significant survival advantage over that seen with chemotherapy alone.

Adjuvant chemotherapy

The CONKO-001 trial randomized 368 patients, of whom 179 were randomised to adjuvant gemcitabine and included in the primary analysis (intent-to-treat) and 175 randomised to surgery alone and included in the primary analysis and reported in 2007. The primary end point was disease free survival (DFS). The median (95% CI) DFS for gemcitabine was 13.4 (11.4, 15.3) months and 6.9 (6.1–7.8) months for surgery alone (p < 0.001, log-rank). The estimated DFS at 3 and 5 years was 23.5% and 16.5% respectively in the gemcitabine group and 7.5% and 5.5% respectively in the control group. By December 1st 2007 303 events (85.6%) have occurred for DFS and 293 events (82.8%) for overall survival (19). Gemcitabine significantly improved the median overall survival (22.8 months) compared to the surgery alone group (20.2 months; p = 0.005) with estimated survival at 3 and

5 years of 36.5% and 21.0% respectively for the gemcitabine group vs. 19.5% and 9.0% respectively for the surgery alone. The results from ESPAC-1 formed the basis of the ESPAC-3(v2) trial which was designed to identify if either adjuvant gemcitabine or 5-FU/FA was associated with significant better survival in patients with resected pancreatic cancer. The trial randomised 1030 patients with an R0/R1 resection for pancreatic ductal adenocarcinoma who received adjuvant therapy within 8 weeks of surgery. The final two year analysis demonstrated median survival from resection of patients treated with 5-FU/FA was 23.0 (95% CI: 21.1, 25.0) months and for patients treated with gemcitabine this was 23.6 (95%CI: 21.4, 26.4) months. Log-rank analysis revealed no statistically significant difference in survival estimates between the treatment groups ($c2LR = 0.7$; $p = 0.39$; $HRGEM = 0.94$; 95% CI: 0.81, 1.08). There was no significant difference in the effect of treatment across subgroups according to R status (test of heterogeneity $c21 = 0.3$, $p = 0.56$). These results (20) provide the rationale for the use of gemcitabine as the control arm in ESPAC-4 trial.

Combination chemotherapy
There is now mounting evidence that combination therapy with gemcitabine is superior to gemcitabine alone in patients with advanced pancreatic cancer. The combinations of gemcitabine and erlotinib (epidermal growth factor receptor tyrosine kinase inhibitor) or platinum based analogues or capecitabine have proven to be superior to gemcitabine alone. The strongest evidence comes from the GemCap study. The GEM-CAP regimen was shown to significantly improved objective response rate (19.1% vs. 12.4% respectively; $p = 0.034$) and progression-free survival (HR = 0.78; 95% CI: 0.66, 0.93; $p = 0.004$) and was associated with a trend toward improved overall survival (HR = 0.86; 95% CI: 0.72, 1.02; $p = 0.08$) compared with gemcitabine alone. A meta-analysis of two additional studies involving 935 patients showed a significant survival benefit in favor of GEM-CAP (HR = 0.86; 95% CI: 0.75, 0.98; $p = 0.02$) with no inter-trial heterogeneity.

ESPAC-4
Long term survival following resection for pancreatic cancer still needs to be improved. Adjuvant 5-FU/FA demonstrates significant improvement in overall survival following surgery; adjuvant gemcitabine also demonstrates a survival advantage following surgical resection for pancreatic cancer. Gemcitabine plus capecitabine improves survival in patients with advanced pancreatic cancer compared with single agent gemcitabine. The ESPAC-4 trial aims to answer the question whether there is a survival difference between a single agent (gemcitabine) versus combination chemotherapy (gemcitabine plus capecitabine) in patients following resection for pancreatic cancer.
The study will randomise patients following pancreatic cancer resection surgery to gemcitabine plus capecitabine versus gemcitabine. The primary outcome measure is overall survival.

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