M65 were compared with Wilcoxon test. Means of the difference between M30 and M65 values before and after chemotherapy were calculated then prognostic significance of these increments for survival was evaluated by univariate and multivariate. Logistic regression analysis was performed to predict response to chemotherapy.
Results: Serum M30 and M65 levels were significantly found to be increased after chemotherapy (M30, pre- 582.7±111.5 U/L vs. postchemotherapy 983.3±214.1 U/L, p = 0.01; M65, pre- 2061.7±431.2 U/L vs. postchemotherapy 2646.3±433.1 U/L, p = 0.003). Means of the difference M30 and M65 levels before and 48 hours after chemotherapy were 400.5±190 U/L [(M30-difference) M30-D)] and 584.6±335.4 U/L (M65-D), respectively. Patients whose serum M30-D ⩽400.5 U/L had better median PFS and OS times than patients with M30-D >400.5 U/L (PFS, 7 vs. 3.1 months, p = 0.004 and OS, 8.2 vs. 4.1 months, p = 0.002). In addition, median PFS and OS intervals in patients with serum M65-D >584.6 U/L were significantly worse than those of patients whose M65-D was lower than or equal to 584.6 U/L (PFS, 7 vs. 4.7 months, p = 0.004 and OS, 8.2 vs. 4.7 months, p = 0.002). Patients with increased M30-D and M65-D had better tumour response compared to patients with low M30- and M65-D (p = 0.02 and p = 0.006, respectively). In the logistic regression analysis, only M65-D was significantly found to be an independent factor in predicting response to chemotherapy (p = 0.018, OR:1.4). However, prognostic significance of M30 and M65 levels before and after chemotherapy could not be proved in the multivariate analysis.
Conclusions: These results showed for the first time that both M30 and M65 in serum samples of patients with advanced gastric cancer were elevated 48 hours after chemotherapy and these were poor prognostic factor for PFS and OS of patients. Moreover, increased plasma M65 level after chemotherapy can be predict tumour response.

6611 POSTER

MUC4 Expression as a Prognostic Factor in Gastric Cancer − Clinicopathologically Significant Only in the Intestinal Phenotype

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Background: Gastric cancer is histologically classified into two types, intestinal and diffuse type, based on the gland formation tendency. Mucins are high molecular weight glycoproteins that play important roles in carcinogenesis and tumour invasion. Claudins are the proteins that participate in the formation of tight junctions. Tight junction proteins are believed to be involved in the regulation of proliferation, differentiation, and other cellular functions. Expression of mucin and claudin family in gastric cancers has been studied by many laboratories, but the results are conflicting. Therefore, we investigated the potential of MUC and claudin family to be used as a prognostic marker in gastric cancer according to histologic subtype.
Methods: Three-hundred sixty-five gastric adenocarcinoma patients who underwent surgical resection and had not received any pre- or -post surgery therapy, were selected for this study. Among the 365 gastric cancer samples tested here, 124 (34%) were early gastric cancer, and 241 (66%) were advanced. Intestinal type was 68.7% and diffuse type was 30.7%. We made tissue microarrays with paraffin-embeded formalin fixed blocks of gastric cancer and these microarrays were evaluated for phenotypic expression of MUC1, MUC4, Claudin 1, 3, 4, 5, 7 and 10 using anti-human rabbit or mouse polyclonal antibody. The expression levels were correlated with key clinicopathologic features and patient outcomes.
Results: There was no significant difference of MUC and claudin expression between early and advanced gastric cancer. Gastric cancer patients with increased MUC4 and claudin 10 expression were significantly associated with better overall survival (p = 0.049, 0.012). When we evaluated accoding to the histologic type, only significant in the intestinal type (p = 0.032). High expression of claudin 1 was associated with better disease free survival. In early gastric carcinoma, high expression of claudin 5 was significantly correlated with poor disease free survival (p = 0.045), but in advanced gastric carcinoma, high expression of claudin 5 was not correlated with poor disease free survival. Low expression of claudin 10 was significantly correlated with poor overall survival (p = 0.021).
Conclusion: Our present findings show that the increased expression of MUC4 could be used as a good prognostic marker in intestinal type gastric cancer. Overexpression of claudin-10 is a prognostic indicator of prolonged survival of patients with early and advanced gastric cancer.

6612 POSTER

The Role of Vascular Endothelial Growth Factor (VEGF) and VEGF-receptors Genotyping in Guiding the Metastatic Process in Radically Resected Gastric Cancer Patients

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Background: In radically resected gastric cancer the possibility to predict the site of relapse could be clinically relevant for the selection of post-surgical management. We previously demonstrated that tumour integrins genotyping is involved in determining the metastatic sites. Preclinical studies suggested that tumour angiogenesis may also be crucial for the metastatic process of gastric cancer cells. We then investigated the role of VEGFs and VEGF receptors genotyping in determining either peritoneal carcinosis or hematogenous metastases in radically resected gastric cancer patients.
Patients and Methods: Genotyping for VEGF-A, VEGF-C and VEGFR-1,2,3 was carried out on pT4a radically resected gastric tumours recurring with either peritoneal-only carcinosis or hematogenous metastases. Tumour genotyping for integrins was also performed according to our previous findings.
Results: 101 patients fulfilled the inclusion criteria: 57 with peritoneal carcinomatosis only and 44 with hematogenous spread only. At multivariate analysis, intestinal histology and the AC genotype of rs699947 (VEGFA) showed to independently correlate with hematogenous metastases, whereas diffuse histology and the AA genotype of rs2269772 (ITGA) independently correlated with peritoneal-only diffusion (p = 0.001) (Table 1).
Conclusions: Our results seem to indicate that combining information from genotyping of rs699947 (VEGFA, AC), rs2269772 (ITGA, AA) and tumour histology could allow clinicians to individuate gastric cancer at high risk for recurrence either with peritoneal or hematogenous metastases. The selection tool deriving from this analysis may allow an optimal use of the available treatment strategies in these patients.

Table 1

	rs10434 (VEGFA, G > A)			
	GG	**GA**	**AA**	**ND**
Peritoneal carcinosis, n (%)	16 (28)	30 (53)	5 (9)	6 (10)
Hematogenous metastases, n (%)	11 (25)	20 (46)	12 (27)	1 (2)
p	n.s.	n.s.	0.0282	
	rs699947 (VEGFA, A > C)			
	AA	**AC**	**CC**	**ND**
Peritoneal carcinosis, n (%)	9 (16)	17 (30)	26 (45)	5 (9)
Hematogenous metastases, n (%)	5 (11)	26 (59)	11 (25)	2 (5)
p	n.s.	0.006	n.s.	
	rs7993418 (FLT1, A > G)			
	AA	**AG**	**GG**	**ND**
Peritoneal carcinosis, n (%)	34 (60)	16 (28)	1 (2)	6 (10)
Hematogenous metastases, n (%)	21 (48)	13 (29)	7 (16)	3 (7)
p	n.s.	n.s.	0.0259	

6613 POSTER

Genetic Polymorphism of Biotransforming Enzymes and Risk of Pancreatic Cancer

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Background: The incidence of pancreatic cancer (PC) in the Czech Republic is highest in the world. Both genetic and enviromental factors may be involved in pancreatic carcinogenesis. Genetic and enviromental factors may also interact, e.g. when polymorphism of biotransforming enzymes is associated with increased susceptibility enviromental chemical mutagens. PC remains an incurable disease in most patients. Preventive strategies aim to identify the population at risk that could be followed more closely in screening programs. In addition, elimination of enviromental risk factors or chemopreventive strategie could be studied in high risk population. The present study was focused on gene polymorphisms in biotransforming enzymes in PC patients.
Materials and Methods: 278 PC patients and 403 healthy controls were studied. Gene polymorphisms of following biotransforming enzymes was investigated: CYP1B1, EPHX, NQO1 GSTP1, GSTT1 and GSTM1. DNA was amplified by PCR, subsequently split by restriction enzymes, and the

restriction fragment size was identified by horizontal electrophoresis. The survival was determined using Kaplan–Meier method, and the log-rank test was used for evaluation of differences in survival. The association between genetic factors and cancer risk were analyzed by logistic regression, and the results were expressed as odds ratios (OR) and 95% confidence intervals (CI). Statistical analyses were performed using CRAN 2.4.0 statistical software, and the decision on significance was based on $p < 0.05$.
Results: Comparison of allele distribution between PC patients and controls demonstrated that Val/Val genotype carriers in codon 432 CYP1B1 had lower PC risk of pancreatic cancer development compared wild type carriers (OR 0.59; 95% CI 0.36–0.96; $p = 0.035$). Heterozygotes also had lower risk (OR 0.69; 95% CI 0.49–0.97; $p = 0.033$). There was an even more signficant increase of risk in patients who had histologically verified PC. Variant allele in GSTP1 codone 105 was associated with a trend of higher PC risk (OR 1.38; 95% CI 0.96–1.97, $p < 0.05$). Increased PC risk was also observed for GSTT1deletion (OR 1.56; 95% CI 0.93–2.61, $p < 0.05$). The combination of GSTT1 mutation and GSTP1 deletion was associted with significantly increased PC risk (OR 2.5; 95% CI 1.20–5.20; $p < 0.05$). No significant association was observed between the polymorphism of other biotransforming genes and PC risk, and none of the gene polymorphisms investigated was associated with differences in PC survival.
Conclusions: Gene polymorphism of biotransforming genes may be associated with the risk of PC.

6614 POSTER

Clinicopathologic Significance of Expression of Nuclear Factor Kappa B and Its Target Gene Products in Gastric Cancer Patients

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Background: Nuclear factor-κB (NF-κB) is involved in cell proliferation, invasion, angiogenesis and metastases by activating or repressing NF-kB target genes. The principal objective of this study was to assess the prognostic significance of NF-κB and its target genes in gastric cancer.
Methods: The tumour tissues of 115 patients with gastric cancer were immunohistochemically evaluated using monoclonal antibodies against NF-κB. Preoperative serum levels of vascular endothelial growth factor (VEGF), interleukin-6 (IL-6) were assessed via Enzyme-Linked Immuno-Sorbent Assay (ELISA). C-reactive protein (CRP) and serum amyloid A (SAA) were measured via immunotrubidimetry.
Results: Positive rate of NF-κB was 42.6%. NF-kB expression was related to tumour size, depth of invasion, lymph node metastasis, stage, and lymphovascular invasion. NF-κB expression in tumour tissues was also related to serum levels of IL-6 ($p = 0.044$) and CRP ($p = 0.010$). IL-6, SAA, CRP were related to depth of invasion, VEGF and SAA were correlated with lymph node metastasis. IL-6, VEGF, SAA and CRP were related to the TNM stage. Univariate analysis demonstrated that immunostaining of NF-κB, levels of CEA, CA19-9, IL-6, VEGF, SAA were significantly related with both disease free survival and overall survival. Multivariate analysis verified that NF-κB (Hazard ratio: 3.40, $p = 0.024$) and SAA (Hazard ratio: 3.39, $p = 0.045$) were independently associated with overall survival.
Conclusions: Immunohistochemical staining of NF-κB expression was related to serum levels of target gene products. Serum levels of IL-6, VEGF, SAA, and CRP might be markers TNM stage. Increased expression of NA-κB and high levels of SAA were associated with poor overall survival in gastric cancer patients.

6615 POSTER

Derangement HNF4a Expression as a Candidate Marker of Hepatocellular Carcinoma Progression

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Hepatocyte nuclear factor 4 (HNF4)α is a nuclear receptor playing a key role in hepatic differentiation. This gene is transcribed from two distinct promoters, whose activity results in expression of two groups of isoforms and reflects the level of hepatocytes differentiation. HNF4αP2 isoforms are prevalent in embryonic liver, while HNF4αP1 become predominant in mature hepatocytes. According to our previous surveys, hepatocellular carcinoma (HCC) progression is associated with the deregulation of HNF4α. Investigations on the collection of chemically induced mouse HCCs of independent origin revealed strict correlation of HNF4α expression with tumour differentiation state. To examine whether alterations of HNF4α gene expression are representative for human primary liver tumours we have analyzed the synthesis of HNF4α isoforms in 37 cases of human HCC on the paraffin sections by immunohistochemical staining.
Intracellular localization and protein expression level of HNF4α isoforms were investigated immunohistochemically using specific antibodies for HNF4αP1 or HNF4αP2 groups of isoforms. HNF4α isoforms immunoreactivity was detectable in all studied tumours except few severely dedifferentiated cases. Nuclear staining of tumour cells with HNF4αP1 specific antibodies was less intensive than in normal hepatocytes. Activation of HNF4αP2 isoform, uncharacterisic for adult hepatocytes, was found in tumours (92% of cases) and surrounding liver tissue (56% of cases). We suppose that HCC progression is accompanied with activation of HNF4αP2 isoforms, decreased HNF4αP1 synthesis while in severely dedifferentiated tumours the expression of both groups of HNF4α isoforms is repressed. In order to investigate the possibility of using alterations in HNF4α isoforms expression as a prognostic factor for the HCC treatment, the pilot multifactor analysis of long-term survival after surgical HCC treatment were carried out. Maintenance of HNF4αP1 isoforms synthesis was found to be statistically reliable factor associated with overall survival. We expect that further analysis of correlation between tumour differentiation and patients postoperative survival rate with the pattern of HNF4α isoforms expression on the expanded collections of human HCCs archival samples would allow to estimate the possible impact of HNF4α expression analysis for HCC diagnostics and prognosis.
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6616 POSTER

Impact of Progression on Resource Utilization in the Treatment of NET

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Background: Neuroendocrine tumours (NET) are associated with high morbidity and mortality; however, literature on resource utilization with progression is scarce. The aim of this study was to compare resource use in advanced NET patients at diagnosis versus post-progression.
Materials and Methods: An online survey was administered to physicians in the US, UK, Germany, France, Brazil and Italy. The survey collected resource utilization during the baseline period (time post-diagnosis but pre-progression; 12.8 months), 1st (8.7 months), and 2nd progression (12 months). Progression was defined as measurable/ radiographic evidence of tumour progression.
Results: Of 4,100 surveys administered, 197 physicians participated (4.8%), providing data on 394 patients. NET subtypes included GI (45%), lung (24%), and pancreas (31%). Resource utilization consistently increased from baseline through progression (Table 1).

Table 1. Resource utilization at baseline vs. post progression

	Baseline			Any Progression*		
	All NET % (N = 377)	GI/Lung % (N = 264)	Pancreas % (N = 113)	All NET % (N = 640)	GI/Lung % (N = 442)	Pancreas % (N = 198)
Chemotherapy	21.8 (82)	23.9(63)	16.8 (19)	29.2 (187)	30.3 (134)	26.8 (53)
PRRT	1.9 (7)	1.9 (5)	1.8 (2)	6.1 (39)	6.3 (28)	5.6 (11)
Somatostatin analogs	61.0 (230)	61.7 (163)	59.3 (67)	48.0 (307)	48.4 (214)	47.0 (93)
Routine Monitoring						
Ultrasound	52.5 (198)	50.0 (132)	58.4 (66)	40.2 (257)	39.1 (173)	42.4 (84)
CT scans (conventional or helical)	84.9 (320)	86.4 (228)	81.4 (92)	81.6 (522)	82.8 (366)	78.8(156)
Other imaging†	49.6 (187)	48.1 (127)	53.1 (60)	34.4 (220)	33.5 (148)	36.4 (72)
Biomarkers	69.0 (260)	68.2(180)	70.8 (80)	55.2 (353)	54.1(239)	57.6 (114)
Lab tests	56.2 (212)	52.6(139)	64.6 (73)	46.9 (300)	43.4(192)	54.6 (108)
Visits (surveyed physicians)	97.1 (366)	96.6 (255)	98.2 (111)	96.3 (616)	95.7 (423)	97.5 (193)
Hospitalizations	37.1 (140)	36.0 (95)	39.8 (45)	43.9 (281)	43.0 (190)	46.0 (91)
Surgery	28.7 (108)	26.5 (70)	33.6 (38)	23.9 (153)	23.1 (102)	25.8 (51)
Targeted therapies Dagger;	1.3 (5)	1.1 (3)	1.8 (2)	3.9(25)	2.9 (13)	6.1(12)

*1st and assumed 2nd progression, potentially resulting in multiple events per patient.
† PET, SRS, mIBG, MRI, Chest X-Ray.
Dagger; Everolimus, sunitinib, imatinib, bevacizumab.

Conclusions: Recent recommendations propose that progression free survival should be the primary endpoint in clinical trials in NET. It is therefore important to characterize the impact that progression has in the