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PO13
DNA methylation of the homeobox genes PITX2 and SHOX2 predicts outcome in non small cell lung cancer patients
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Background. Biomarkers that facilitate prediction of disease progression in lung cancer patients might be clinically valuable in optimizing individualized therapy. In this study, the ability of DNA methylation biomarkers PITX2 and SHOX2 to predict disease outcome in lung cancer patients was evaluated.

Methods. Quantitative, methylation-specific (HeavyMethyTM) real time PCR assays were used to measure DNA methylation of PITX2 and SHOX2 in formalin-fixed, paraffin-embedded tissues from 474 non-small-cell lung cancer patients.

Results. In univariate Cox's Proportional Hazard analysis, SHOX2 and PITX2 hypomethylation were significant predictors for disease progression (SHOX2: n=465, HR=1.395 [1.330-1.471], p=0.002; PITX2: n=445, HR=1.312 [1.059-1.625], p=0.013). Patients with hypomethylation of either PITX2 and/or SHOX2 (n=310) showed a significantly higher risk of disease progression as compared to patients with hypermethylation of both genes (n=166; HR=1.555 [1.100-2.199], p=0.001). This was particularly true for the subgroup of patients receiving no adjuvant radio- or chemotherapy (n=258, HR=1.852 [1.522-2.298], p=0.002). In multivariate analysis, both biomarkers added significant independent prognostic information to pT, pN, pM, and grade. In addition, SHOX2 and PITX2 DNA methylation were shown to be inversely correlated with TTF1 (also known as NKX2-1) expression (PITX2: p=0.018, SHOX2: p<0.001).

Conclusions. DNA methylation of PITX2 and SHOX2 are independent prognostic biomarkers for disease progression in non-small cell lung cancer patients.

PO14
Impact of the new immunohistochemical panel for the diagnosis of lung cancer on overall patients outcome
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Background. The availability of targeted therapies created the need for precise subtyping of lung cancers. Aim of the study is to analyse the impact of the new immunohistochemical diagnostic panel on incidence and survival of lung cancer patients by histotypes.

Methods. Patients were selected from the Ticino Cancer Registry and categorized into the four WHO-defined histotypes. 2-year overall survival (OS) was performed for patients with a 24-month complete follow-up (incidence period 1996-2008). Trend analysis of survival probability was computed.

Results. 2,467 lung cancers were selected: 40.4% adenocarcinoma; 21.2% large cell carcinoma, 15.3% small cell carcinoma, 23.9% squamous cell carcinoma. We observed an increasing trend of 2-year OS of all cases, an improved and decreased OS in SqCC and LCC, respectively.

Conclusions. The introduction of an immunohistochemical panel could have influenced not only the incidence of different lung cancer subtypes, but also the short-term outcome of patients, raising the need for

PO12
Glypican-3 expression in non-tumoral liver samples
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Background. Glypican-3 is overexpressed in most hepatocellular carcinoma (HCC) and used as a diagnostic marker of HCC. Recently, Glypican-3 has been shown to be expressed in liver tissue of chronic hepatitis C virus (HCV) infection. This study was aimed to investigate Glypican-3 expression as a predictive marker for development of HCC in patients with chronic HCV infection.

Methods. Needle biopsies of non-tumoral liver tissue of chronic HCV patients with contemporary HCC (n=21) were stained for Glypican-3 expression by immunohistochemistry. Similarly, needle biopsies of liver tissue of chronic HCV patients, that did not develop a HCC for following 5 years (n=21) and were non-responders to therapy were stained for Glypican-3. Using a 0-3+ scale, the staining was described in both groups as normal (-negative), + staining (<50% of cells), 2+ staining (10-25% of cells), or 3+ staining (>25% of cells). All liver samples had severe fibrosis (F3) or cirrhosis (F4).

Results. Liver biopsies were divided into three groups according to activity (METAVIR score A1-A3). Mean score of Glypican-3 expression in non-tumoral tissue of chronic HCV infected patients with contemporary HCC was 2.0 for A1, 1.1 for A2 and 1.8 for A3. Chronically infected HCV patients with A1 had a score of 0-25, A2 of 0-25 and A3 of 0-25. Conclusions. There was a trend of non-tumoral tissue from chronic HCV infected patients with non-tumoral tissue towards a higher Glypican-3 expression. However, no statistically significant difference was observed between the two groups. Glypican-3 expression correlated better with the grade of activity.
cautious interpretations of previous studies and clinical trials where the diagnosis of lung cancers was based on histological evaluation without ancillary immunohistochemical studies.

**PO15**

**LICAM protein expression is associated with poor prognosis in non-small cell lung cancer**

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**Background.** The L1-cell adhesion molecule (LICAM) is potentially involved in epithelial-mesenchymal-transition (EMT) which is important for non-small cell lung cancer (NSCLC) prognosis. The relevance of LICAM for NSCLC is unclear. We investigated the protein expression of LICAM in a cohort of NSCLC patients and correlated LICAM expression with clinicopathological parameters including survival of patients and markers of epithelial-mesenchymal-transition.

**Methods.** Tumors of 468 patients with surgically resected NSCLC were analyzed for expression of LICAM, E-cadherin, β-catenin, slug, and vimentin by semi-quantitative immunohistochemistry. Lung cancer cell lines were evaluated on mRNA and protein level for expression of EMT related markers after stimulation with TGF-β1, Matrigel invasion after TGF-β1 stimulation and after LICAM knockdown by siRNA was tested.

**Results.** LICAM protein expression was found in 25% of squamous cell carcinomas and 24% of adenocarcinomas and correlated with blood vessel invasion and metastasis (<0.05). LICAM was an independent predictor of survival in a multivariate analysis including PT, pN, and pM categories, and tumor differentiation grade. LICAM expression was positively correlated with vimentin, β-catenin, and slug, but inversely with E-cadherin (all p-values <0.05). E-cadherin expression was higher in the tumor center, whereas LICAM and vimentin were highly expressed at the tumor-stroma interface. In LICAM-negative A549 cells the LICAM expression was upregulated and matrigel invasion was increased after stimulation with TGF-β1. In LICAM-positive SK-LU-1 and SK-LC-L1 cells the invasion was decreased after LICAM siRNA knockdown.

**Conclusions.** LICAM is a novel prognostic marker for NSCLCs that is upregulated by EMT induction and appears to be instrumental for enhanced cell invasion.

**PO17**

**Immunohistochemical discrimination between symplastic (bizarre) leiomyoma and leiomyosarcoma of the uterus**

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**Background.** Symplastic (bizarre) leiomyomas of the uterus can show a wide range of histomorphologic changes such as high cellularity, intermediate mitotic count (up to 8/10HPF) and bizarre atypical cells mimicking leiomyosarcoma. In the absence of tumor necrosis, discrimination between symplastic leiomyomas and leiomyosarcomas can be difficult. Discrimination between these two entities with immunohistochemical staining has been described with discordant results.

**Methods.** A tissue microarray of 70 cases including 34 usual leiomyomas, 11 cellular leiomyomas, 9 symplastic leiomyomas and 16 leiomyosarcomas diagnosed between 1991 and 2008 was constructed. In addition to H&E and toluidine blue staining, immunohistochemistry for 14 different markers was performed, namely MCT, c-kit, LCA, MIB-1, CD3, p105, p53, bcl2, ER, PgR, SMA, Actin, Desmin and Myoglobin. The percentage of positive stained cells was assessed and staining intensity was scored as weak (1), moderate (2) and strong (3).

**Results.** None of the markers alone could clearly distinguish between leiomyosarcomas and symplastic leiomyomas. Expression of PgR and Desmin was lower by trend in leiomyosarcomas compared to the three other groups, whereas expression of P16 was higher in leiomyosarcomas. The combination of a PgR >50% and P16 expression in >50% or the combination of PgR in <35% and Desmin expression in >50% clearly distinguished between symplastic leiomyomas and leiomyosarcomas (<0.001).

**Conclusions.** Tumour necrosis and a high mitotic count are the best indicators for leiomyosarcoma. If these indicators are absent, combination of PgR, Desmin and P16 expression might help to distinguish between leiomyosarcoma and symplastic leiomyoma of the uterus.

**PO16**

**Cyclin D1 is a prognostic and predictive marker in metastasizing bladder cancer**

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**Background.** Amplification rate, expression level and prognostic and predictive impact of Cyclin D1 in metastasizing bladder cancers are unknown.

**Methods.** Hundred and fifty lymph node positive patients with urothelial bladder cancer underwent cystectomy and lymphadenectomy. Tissue microarrays were constructed with four tumor samples per patient, two each from the primary tumor and from metastases. Cyclin D1 gene (CCND1) was evaluated by fluorescence in-situ hybridisation (FISH) and the protein by immunohistochemistry.

**Results.** CCND1 amplification was similar in primary tumors (18%) and metastases (21%) and highly homogeneous in both tumor components (kappa: 0.8 and 0.9). Cyclin D1 expression was significantly higher in amplified compared to non-amplified cancers (<0.001); however, among the 25% of tumors with highest Cyclin D1 expression only half were amplified. CCND1 amplification in primary tumors and Cyclin D1 overexpression in metastases were independent predictors of early death (<0.02 each). The latter information was lost after chemotherapy.

**Conclusions.** CCND1 amplification is an important but not the only mechanism for Cyclin D1 overexpression in bladder cancer. CCND1 and Cyclin D1 protein status add independent prognostic information. High Cyclin D1 expression in the metastases predicts response to chemotherapy.

**PO18**

**Sentinel node in melanoma: predictive significance on survival**

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**Background.** Sentinel node (SN) status is the most important prognostic factor for early-stage melanoma patients. It will influence follow-up and may change therapy. The aim of this study was to evaluate survival in patients with minimally invaded and negative SNs.

**Methods.** SN biopsy (SNB) was performed in 449 clinically No patients between 1997 and 2008 in our institution. Positive SNs were pathologically re-assessed for tumor burden (<0.1 mm, 0.1-1.0 mm, and >1.0 mm), and microanatomic location (subcapsular, combined subcapsular and parenchymal, parenchymal, multifocal, or extensive). Minimally invaded SNs were defined as those with tumor burden <0.1 mm and/or subcapsular location.