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Abstracts

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Group 1: Oral Presentations (OP) part 1 and 2

OP-101. 402 HPV Subtyping Results Comparing Smears, Biopsies and Conisations

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Background: The link between squamous cell cervical carcinoma and HPV is well-established and screening methodes have developed rapidly during the last decade, provoked by molecular HPV subtyping. Most commercially available tests for HPV subtyping are able to distinquish between low and high risk HPV infection, but a list of particular HPV subtypes is missing. Here we present a study on 402 cases, where a macroarray analyzes 32 HPV types. We compared cytology specimens and histological ones like biopsies, cones and loop excisions.
Methods: GP5+/GP6+ and My11/9 primed PCRs were performed followed by subtyping 16 high and 16 low risk HPV types by a macroarray of Chipron.
Results: HPV 16, 31 and 51 are the predominant high risk types, HPV 42 and 53 the most common low risk types. In 49, 1% there is a single HPV infection, whereas in 27, 2% a dual and in 12,8% a triple one. We observed up to 9-fold infections. In 71, 8% there is an identical subtyping result in pap smears and biopsies. In 21, 6% the smear subtpyping yielded additional subtypes, only in 5, 5% biopsies were more sensitive. Cytological controls after conisation exhibit a HPV infection in nearly one half of the cases, sometimes HPV subtypes constellation do differ from the original ones.
Conclusions: Cytological sampling is the method of choice for HPV subtyping in cervical screening. HPV clearing is not achieved satisfactory by conisation. Therefore subtyping of HPV should be discussed as a standard procedure in addition to cytological controls.

OP-102. HPV in Tonsillar Carcinoma

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Background: HPV has been implicated as causative agent in head and neck carcinomas. The biology of HPV tumours seems to differ from alcohol and tobacco related tumours.
Methods: Formalin fixed and paraffin embedded tissue of tonsillar carcinomas of 83 patients was retrieved from the archives of the Pathological Institute. 76 of 83 patients had been treated at the Dept. of Radiation Oncology between 1997 an 2008 either primarily or in an adjuvant setting. HPV status was analysed by multiplex PCR and direct sequencing. The results were entered into clinico-pathological correlation.
Results: HPV was found in 34/83 cases (41%), in 33 cases HPV-16, in one case HPV-33. 9 HPV-16 positive tumours harboured additional HPV-types (35, 45, 51, 59). Positive HPV status was most prevalent in basaloid carcinomas (11/13 cases, 85%) compared to keratinizing and non-keratinizing squamous cell carcinomas and lymphoepithelial carcinomas (HPV positivity in 18%, 42% and 33%). TNM-tumour stage of HPV positive cases was significantly lower. Comparison with clinical data showed an inverse correlation between HPV and alcohol consumption and cigarette smoking. In multivariate analysis positive HPV status as well as non-smoking and tumour-free resection margins were favourable prognostic factors. HPV positivity was associated with prolonged overall and disease free survival.
Conclusions: HPV seems to be an important causative factor in tonsillar carcinomas. Although most prevalent in basaloid carcinomas, it can be detected in all histological types. HPV positive cases are associated with favourable prognosis which may be due to increased radiosensitivity

OP-103. Poorly Differentiated Thyroid Carcinoma – How Much Poorly is Needed?

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Background: Poorly differentiated carcinomas of the thyroid (PD) are conceptually situated in between classic papillary and follicular carcinomas and anaplastic thyroid carcinomas. Today, it is not clear, how much of a PD area in a given tumor is required to allow such a diagnosis.
Methods: We identified via the nuclear medicine departments all patients with a carcinoma of the thyroid with an adverse clinical outcome, defined as more than one relapse or tumor associated death. We estimated the area of a poor differentiation per tumor, according to the Turin criteria of PD carcinomas (solid/trabecular/insular growth pattern; lack of nuclei of papillary carcinoma and one of the following: 1. convoluted nuclei, 2. tumor necrosis, 3. three or more mitoses per ten high power fields).
Results: We examined 92 Patients and correlated the results with the overall survival (OS), tumor specific survival (TSS) and relapse free survival (RFS). With a cut-off of 10%, we identified 35 PD carcinomas. 57 age, stage and gender matched classic follicular carcinomas served as controls. Even with only a small 10% of the area being poorly differentiated, the OS, TSS and RFS in a Kaplan-Meier analysis was significantly worse than in the control group ($p<0.001$). In a multivariate analysis including age, gender, tumor stage and PD area above 10% for OS, TSS and RFS, the only consistent significant factor was PD ($p<0.001$).
Conclusions: Even very minor PD part in a thyroid carcinoma affects prognosis significant. The presence of such areas may be worth reporting in thyroid carcinomas.

OP-104. Prognostic Role of CD68-Positive Macrophages in the Context of the Reactive Environment of Classical Hodgkin Lymphoma (HL)

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Background: HL consists of neoplastic Hodgkin and Reed-Sternberg cells (HRSC) and a micromilieu of non-neoplastic cells that greatly outnumber the HRSC. Studies on HRSC-related prognostic biomarkers were largely unsuccessful, but the composition of the microenvironment is of prognostic importance. Recently, the number of macrophages has been correlated with adverse survival in HL and there was a claim for results validation.
Methods: We analyzed the prognostic importance of the CD68-positive macrophage number compared to other cellular environmental components in an unselected series of 105 HL in tissue microarrays by immunohistochemistry.
Results: Applying a cut-off score of >0.82% tumor macrophages, cases with increased numbers showed worse overall survival (mean 185 months, median 192) compared to cases with lower amounts (mean 285 months, median not reached). Eleven of 62 patients with ≤0.82% macrophages died compared to 19 of 43 with >0.82% ($p<0.001$). Importantly eight of the latter died of a second malignancy. The number of macrophages correlated with low FOXP3/high Granzyme B/high PD-1-positive cellular background and with patient age, and was not of independent prognostic significance in our collective. However, a combination background score with all negative prognostic microenvironmental components (CD68-, PD-1- and Granzyme B-positive cells) was of independent prognostic significance ($p=0.002$, relative risk 2.63).
Conclusions: The reactive non-neoplastic micromilieu is of decisive prognostic importance in HL. An increased number of macrophages is associated with an adverse outcome. However, the number of macrophages is probably only a part of a complex interaction network of reactive immune cells, especially T-cell subsets, in HL.

OP-105. SDHB Loss Predicts Malignancy in Pheochromocytomas/Sympathethic Paragangliomas, but not through Hypoxia Signalling

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Background: Prediction of malignant behaviour of pheochromocytomas/sympathetic paragangliomas (PCC/PGL) is very difficult if not impossible on a histopathological basis. In a familial setting, it is well known that SDHB-associated PCC/PGL very often metastasize. Recently, absence of SDHB expression as measured via immunohistochemistry was shown to be an excellent indicator of the presence of an SDH germline mutation in PCC/PGL. SDHB loss is believed to lead to tumour formation by activation of hypoxia signals.
Methods: To clarify the potential use of SDHB immunohistochemistry as a marker of malignancy in PCC/PGL and its association with classic hypoxia signalling we examined SDHB, Hif-1alpha and its targets CA-9 and GLUT-1 expression on protein level using immunohistochemistry on a tissue micro array on a series of familial and sporadic tumours of 115 patients. Survival data was available for 66 patients.
Results: SDHB protein expression was lost in the tumour tissue of 12 of 99 patients. Of those 12 patients 5 had an SDHB germline mutation, in 5 patients no germline mutation was detected and mutational status remained unknown in parts in 2 patients. Loss of SDHB expression was not associated with increased classic hypoxia signalling as detected by HIF-1alpha, CA-9 or GLUT-1 staining. Loss of SDHB expression was associated with an adverse outcome.
Conclusions: The lack of correlation of SDHB loss with classic hypoxia signals argues against the current hypoxia hypothesis in malignant PCC/PGL. We suggest SDHB protein loss as a marker of adverse outcome both in sporadic and in familial PCC/PGL.

OP-106. Absence of Extramural Venous Invasion is an Excellent Predictor of Metastasis-free Survival in Colorectal Carcinoma Stage II – A Study using Tangential Tissue Sectioning

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Background: Patients with colorectal carcinoma (CRC) stage II pose a significant therapeutic management problem, since considerable controversy exists regarding the role of adjuvant chemotherapy. Patients with a high risk profile may benefit from adjuvant chemotherapy but the recognition of these patients is difficult. Extramural venous invasion (EVI) is an established risk factor of hematogenous metastasis. However, published incidence rates of EVI of 8.7–33% indicate major technical inconsistencies in the assessment of this important parameter. The present study applies tangential vessel preparation and correlates results with hematogenous metastasis.
Methods: CRC stage II diagnosed between 1994 and 1996 were included in our study. Resection specimens were analyzed by tangential sectioning of the tumor periphery. Confirmation of haematogenous metastasis was assessed by computer tomography, ultrasound and biopsy. The median follow-up period for patients in stage II without metachronous hematogenous metastasis was 49 months.
Results: EVI was detected in 50/79 (63%) CRC stage II. 13/50 (26%) of these patients developed metachronous hematogenous metastasis. The rate of hematogenous metastasis for patients with venous invasion was virtually independent of adjuvant chemotherapy. Only 1/29 patients without EVI (3.5%) progressed to hematogenous metastasis. Absence of extramural venous invasion is significantly associated with metastasis-free survival ($p<0.011$).
Conclusion: EVI is an excellent predictor of tumor progression in CRC stage II. In particular absence of extramural venous invasion is a highly specific (93%) negative predictor of metastasis. However, this is only true if the incidence of EVI is assessed properly by tangential sectioning of the tumor periphery.

OP-207. VEGFA Gene Amplification and Protein Expression in Breast Cancer

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Background: The vascular endothelial growth factor A (VEGFA) protein is a chemical signaling molecule that is known to be a major factor in the induction of angiogenesis during tumor initiation and progression, and is also a target of anti-angiogenic therapies. Recently, we discovered the genomic amplification of the VEGFA gene in a small subset of colorectal cancers. Aim of this study was to investigate the presence of VEGFA gene amplification in breast cancer and to determine its potential impact on VEGFA protein expression.
Methods: VEGFA gene amplification was evaluated by FISH on a multitumor tissue microarray (MTMA) comprising 132 different tumor types. Further, a small tissue microarray was constructed from breast carcinoma samples whose VEGFA protein concentration had been previously quantified by chemiluminescence (check!). In order to interrogate tissue heterogeneity, VEGFA gene amplification was also analyzed on large tissue sections from 70 primary breast cancers.
Results: We detected VEGFA gene amplification in 2% of the breast cancer samples from the MTMA and in 5% of the breast cancer samples with known VEGFA protein concentration. In addition, 8% of the samples (5 out of 65) were characterized by a high polysomy. Interestingly, elevated VEGFA gene copy number was strongly correlated with higher VEGFA protein levels ($p<0.0001$, check!).
Conclusions: VEGFA gene amplification defines a small subset of breast carcinomas with elevated VEGFA protein expression. Our data suggest that FISH analysis of VEGFA could represent an additional evaluation system for the identification of breast cancer patients who might benefit from anti-VEGFA therapies.