2. collapse with bronchioalveolarcell carcinoma (CwB), 3. adenocarcinoma cells (Cells), 4. fibroblasts (F), and 5. mucus (M). Areas of air-type adenocarcinomas (in 49 cases) demonstrated predominantly C and/or CwB (C/CwB type: in 46 cases). Areas of solid-type adenocarcinomas (in 69 cases), in comparison, demonstrated predominantly Cells and/or Cells/F (Cells/F type: in 66 cases). We noted a statistically significant difference between the histopathological findings of the areas of tumor opacity on mediastinal window images of air-type and solid-type tumors. In 34 cases, Cells/F type adenocarcinomas revealed microscopic evidence of metastasis (pleural involvement, vascular invasion, lymphatic permeation, or lymphnode metastsis). Whereas, no C/CwB type adenocarcinomas cases revealed any microscopic metastasis. The prognosis of C/CwB after resection is better than for Cells/F.

Conclusion: We found that 'Air-type' adenocarcinomas demonstrated C/CwB type, and that 'Solid-type' adenocarcinomas demonastrated Cells/F type. We concluded that the histopathological findings of small pulmonary adenocarcinomas could be classified into two groups: C/CwB type and Cells/F type. The prognosis of C/CwB is better than for Cells/F.

D4-02 **Pathology, Thu, 12:30 - 14:15**

Aneusomy by FISH analysis and histology as predictors of invasive lung cancer in bronchial biopsies from high risk subjects

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Background: The development of Lung Carcinoma (LC) is accompanied by field changes of histological and chromosomal abnormalities in the airway mucosa. Neither histological grade nor markers of chromosomal abnormalities in preneoplastic epithelial lesions have been adequately validated as predictors of invasive LC.

Methods: Histological dysplasia score and chromosomal aneusomy measured by FISH analysis were compared as correlates of invasive LC in a case-control study of 44 individuals with LC (cases) and 90 individuals without LC (controls). We used bronchial biopsy samples from subjects found by LIFE or white light bronchoscopy to have had moderate dysplasia (MD), severe dysplasia (SD) or carcinoma in situ (CIS). Tissue samples were reviewed by the study pathologist, the grades of preneoplastic change were verified and the appropriate areas in each histological slide were selected for FISH analysis. A 4-color FISH probe was used for aneusomy detection targeting centromere 6, 5p15.2, 7p12 (EGFR) and 8q24 (CMYC). Three or more copies for two or more of these DNA targets indicated an aneusomic cell. Premalignant lesions were classified as aneusomic when displaying aneusomic cells above the threshold defined in normal bronchial epithelium (mean + 3 SD).

Results: The population included 104 males and 30 females with a mean age of 64 years and a mean smoking history of 62 pack-years. There was no difference in mean age, sex distribution or pack-years of smoking between LC cases and controls, but cases had a higher frequency of current smokers (p=0.05). Thirty two had CIS as the highest histological grade of mucosal abnormality, 48 had SD and 54 MD. The strongest correlate with invasive LC was CIS by histological examination (OR=12.5, 95% CI 4.1 to 38.1). Chromosomal aneusomy was seen in 64% of the LC cases but in only 31% of the controls. (OR = 4.6, 95% CI 2.0 to 10.9). The proportion of subjects with chromosomal aneusomy increased from moderate dysplasia (22.2%) to severe dysplasia (41.7%) and CIS lesions (71.9%) and showed a similar trend for cases and controls. Presence of aneusomy slightly increased the risk for LC in MD (OR=1.91, 95% CI 0.26 to 13.8) but was a substantial impacting factor in subjects with SD (OR=7.06, 95% CI 0.82 to 60.1) and CIS (OR=5.93, 95% CI 0.5 to 69.7).

Conclusions: CIS on histological examination and abnormal FISH analysis are both associated with lung cancer cross-sectionally. Future studies need to examine these biomarkers prospectively, and to assess their interaction in predicting lung cancer risk.

D4-03 **Pathology, Thu, 12:30 - 14:15**

SCF protein (Skp2, CUL1) regulate the E2F1 dependent transcriptional activity and cyclin E in human lung tumors

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Background: The E2F1 transcription factor is a cell cycle and oncogenic protein which plays ambiguous role in promoting proliferation or apoptosis depending on histological cell type of lung cancer (Salon et al. Cell Death and Differ. 2006). Accordingly, its activity is tightly controlled by transcriptional and post-transcriptional events in which the ubiquitin-proteasome pathway mediated by SCF complexes such as Skp2 and Cullin 1 (CUL1) proteins play a role in its degradation. We have previously identified differential pattern of E2F1 protein expression in human lung cancer with high expression in high grade neuroendocrine tumors, in contrast with low or no expression in non small cell carcinoma and in carcinoids (small cell lung carcinoma and large cell neuroendocrine carcinoma) (Eymin et al. Oncogene 2001). In order to investigate the role of proteasome degradation in E2F1 expression and activity we analyzed the components of SCF complex (Skp2 and CUL1) to understand their role on expression of E2F1 and its transcriptional targets cyclin E, important regulators of cell cycle at G1-S transition.

Methods: Using immunohistochemistry and immunoblotting we analyzed 128 lung tumors of all histological types for the relationship linking E2F1 and two components CUL1 and Skp2 of the ubiquitin-protein ligase SCFSkp2 <involved in E2F1 proteolysis and the consequence on cyclin E level expression.

Results: Skp2 protein was more often overexpressed in high grade neuroendocrine (HGNE) carcinoma (46/54; 86 %) than in NSCLC (16/50; 32 %) (p<0.0001), and undetectable in 25/25 carcinoids. Overexpression of E2F1 and Skp2 proteins were directly correlated in HGNE tumors where Skp2 overexpression was correlated with advanced stage (p<0.0001) and nodal metastasis (p<0.0001). There was a significant correlation between Skp2 and Ki67 across histological types (p=0.01). No correlation was found between E2F1 and CUL1. In in vitro cellular models we provided evidence that Skp2 is a novel transcriptional target of E2F1. Skp2 interacts with E2F1 and stimulates its transcriptional activity toward the cyclin E promoter. Consistently, we found a correlation between Skp2 and cyclin E (p<0.0001) and between E2F1 and cyclin E in neuroendocrine lung tumors (p=0.0001). In contrast, CUL1

correlated with downregulation and low cyclin E level (p=0.0003), and low Ki67 proliferative marker across histological types (p=0.005).

Conclusions: Our data provide the first evident of a direct and functional interconnection linking E2F1, the ratio of Skp2 / CUL1, and cyclin E oncoproteins in human tumors. Whereas Skp2 cooperate with E2F1 to activate its transcriptional function of E2F1 towards cyclin E, CUL1 was identified as a negative regulator of cyclin E suggesting that CUL1 could play a role in limiting the progression of neuroendocrine lung tumors. This indicates therapeutic target for inhibitors of proteasome in high grade neuroendocrine lung tumors.

D4-04 **Pathology, Thu, 12:30 - 14:15**

Useful prognostic factors in small-sized adenocarcinoma

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Background: With the progression of radiologic methodology such as thin section CT and/or high resolution CT, recently we become to diagnose many small-sized adenocarcinoma (less than 2 cm in diameter). In order to diagnose the degree of their malignancy, we need convenient prognostic factors. On the other hand, there are numerous prognostic factors reported those are useful to predict the prognosis of lung non-small cell carcinoma and/or adenocarcinoma. However, the comparison among the factors has not been performed sufficiently, especially about small-sized early adenocarcinoma. This time, we selected 10 immunohistochemical prognostic factors reported before, such as CEA, p53, MIB1, p27, EGFR, pEGFR, Cox2, Neuromatin, γH2AX, and TTF-1 and compared their conveniences using same series of small-sized adenocarcinomas. Furthermore, we also examined the ratio of bronchioloalveolar cell carcinoma (BAC) component and micropapillary component in maximum cut surface of the tumor as histologic factors and genome abnormalities of p53, K-ras, and EGFR were also examined.

Methods: We conducted a retrospective review of 138 consecutive patients who underwent complete resection for small-sized adenocarcinoma and did not receive any chemotherapy and/or radiotherapy prior to surgery in National Cancer Center Hospital (Tokyo, Japan) from January 1993 to December 2000. We selected CEA, p53, MIB1, p27, EGFR, pEGFR, Cox2, Neuromatin, γH2AX and TTF-1 as immunohistochemial prognostic factors. In addition to the factors, we examined the ratio of BAC component and micropapillary component in maximum cut surface of the tumor using H.E. staining sections. Furthermore, p53, EGFR, and K-ras mutation analysis were performed on 78 cases.

Results: Among the 10 immunohistochemical factors, two histological factors, and three genomic factors, CEA, MIB1 index, and BAC component ratio were significantly associated with the prognosis of small-sized adenocarcinomas. Cases stained strongly with anti-CEA antibody showed significantly less favorable prognosis than negative cases (p=0.02). Cases that revealed more than 10% of MIB1 index showed less favorable prognosis than cases less than 10% of the index. And cases with more than 50% of BAC component showed more favorable prognosis than cases with less than 50% of BAC component (p<0.01). However, the other factors were not related with the prognosis.

Conclusion: Although numerous prognostic factors were reported about the lung adenocarcinoma, this study indicated that only three factors, namely, two immunohistochemical factors of CEA and MIB1 index and histological factor of the ratio of BAC component in the maximum cut surface of the tumor were significantly associated with the prognosis of small-sized adenocarcinoma of the lung. In order to construct a desirable and evidence-based selective diagnosis of the cases for reduction surgery, more extended study for searching convenient prognostic factors about small-sized adenocarcinoma should be performed.

D4-05 **Pathology, Thu, 12:30 - 14:15**

Is survival after surgical resection of lung cancer influenced by the presence of atypical adenomatous hyperplasia (AAH)?

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Atypical adenomatous hyperplasia (AAH) is a recognised precursor for peripheral parenchymal-type adenocarcinoma whereby AAH transforms into localised non-mucinous bronchioloalveolar carcinoma, wherein alveolar collapse, stromal fibrosis and invasion develop. In our patient population, AAH has been found in around 12% of lung cancer resections and in 23% of resections for adenocarcinoma. About half reported AAH lesions are solitary, some cases yield between 2-5 lesions but up to 20% show over 5 lesions.

Little is known about the likelihood or rate of transformation of AAH into adenocarcinoma. The few follow-up studies published have involved relatively short follow-up and none have shown any relationship between AAH and survival. We present the first case-control study investigating the survival of patients with AAH in lung resection specimens.

Methods: 116 patients with AAH in their resection specimen were compared with 232 controls without AAH. Cases and controls were matched for tumour histology, T & N stage, age and year of surgery. All cases were treated in the Aberdeen Cardio-Thoracic Surgery Unit, the tertiary specialist referral centre for the north of Scotland. All cases of AAH were detected during routine gross and histological examination of lungs resected for primary carcinoma. All lesions identified on gross examination of 1cm thick parasagittal slices of formalin-inflated lung resections were sampled and/or up to 6 random parenchymal tissue blocks were taken. Survival data were derived from our lung cancer resection database, Cancer Registry and Hospital patient data sources.

Results: Tumour stage, nodal status and histology (WHO 2004) were 100% matched between cases and controls. Median ages were 65.4 (IQR 57.5 - 71.0) and 64.5 (58.3 - 70.2) years respectively for cases and controls. More AAH patients were female (50.9% vs 35.3%, p=0.005). Of those cases with AAH, 15% had more than 5 lesions recorded. As expected, most (69%) of the cases had adenocarcinomas. Median follow-up was 32 months for cases and 30 months for controls (95th centiles 130 and 147 months respectively).

No difference was found in the survival of cases with AAH and controls (Median survival [95% confidence interval], 35 [12.3 - 57.7] months vs 39 [29.0 - 49.0] months respectively, p=0.81). When cases were categorised to identify patients with more than 5 AAH lesions (n=17), median survivals for cases with 1-5 AAH lesions was 36 [11.9 - 60] months while for those with over 5 AAHs it was 22 [0

