Case history:
A 69 years old patient was readmitted to the hospital after resection of the left upper lobe of the lung 4 months before because of SqCLC (T1 N0 R0 M0 L1 V1).
The patient was ex-smoker (50 py). a year before the diagnosis of lung cancer. He had been farmer and locksmith.
At readmission the patient suffered from dyspnoe, chest pain and weight loss. He had medication against cardial insufficiency and corticosteroids (Dexamethason, 8 mg). There was candidiasis of the oral mucosa. Vital capacity was reduced. Chest x-ray revealed ground glass opacity of the left residual lung with destroyed areas (abscess) in the upper part and pleural effusion was seen basally. In the bronchial washing ESBL-producing E. coli was found and treated according to resistance test. Bronchoscopy revealed irregularities of the bronchial mucosa of the residual left-upper-lobe bronchus, suspicious for recurrent cancer.
Endobronchial biopsies from this area were taken (snap-shots). PET scan showed strong enhancement in the left lung, so 9 days after bronchoscopy a transthoracic biopsy was taken.

Diagnosis:
Herpes-simplex-virus (HSV) infection of the bronchial mucosa simulating recurrence of a squamous cell carcinoma.

Discussion
HSV-1 Infection of the Lower Respiratory Tract (LRT)
Herpes simplex virus is a DNA-virus, type 1 primarily infecting skin and respiratory tract, type 2 causing mainly genital infections. HSV-infections are known worldwide, 95% of adults and 50 % of 5 years old children have antibodies against HSV-1,. 10 – 30% of adults are infected by HSV2. [1]
HSV type 1 (and 2) infects airways with predisposing factors, “stressful” conditions[2] and anyhow immunosuppressed patients.[3]

Pathogeneity of the virus
HSV-1 infects epithelial cells, which are entered by fusion of viral envelope with plasma-membrane of the host cell. Transcription of HSV-genes by cellular RNA-polymerase II starts 5- 8 h after infection and causes stop of the host cell’s macromolecule-synthesis. After a short viremia , intraepithalially synthesized viruses enter free ends of sensible and autonomous nerves, move to regional sensory ganglia passing 120-400 mm a day to stay latent up to decades. Moving from one nerve cell to the other the virus can escape humoral antibodies[1]. Herpes viruses are pathogenic by encoding cytokine homolog’s such as vIL-6 (raises acute phase proteins), by encoding for chemokine homolog’s (e.g. CCL3), chemokine receptor homolog’s and chemokine-binding proteins which can inhibit or delay cell migration during inflammation. Herpes viruses also encode homolog’s for CD46 and CD55 – complement regulatory proteins blocking C3 activation, but also CD59 (protectin- inhibits MAC-membrane attack complex – complement components of the lytic pathway). Herpes viruses can disrupt MHC class I expression by blocking peptide uptake into the endoplasmatic reticulum.[4]

Host defense mechanisms - immunology
Innate immune defenses as interferon, natural killer cells and macrophages are involved in the early answer against viral infection.IL-12 and more important IL-18 activate NK-T cells to secrete IFN- gamma, which activates macrophages in one day after infection. Macrophages phagocyte and kill virus-infected cells and produce antiviral factors: TNF-alpha, nitric oxide and IFN-alpha. Nitric oxide seems to play a role in HSV1 induced pneumonia. Macrophage-like plasmacytoid-derived DC2 dendritic cells release interferon following the endosomal recognition of viral RNA. The specific immune system prevents virus spread by IgA, induced by CD4+ helper T (Th) cells, which also induce CD8+ CTLs, preventing reinfection by destroying virus-infected cells through release of perforin and granzyme (Fas-FasL interaction).TNF-alpha can induce intracellular interferon, “clearing” infected cells from the virus and inducing apoptotic death of infected cells. Release of TNF can be induced by CD8+ T-cells and macrophages by CD4+ Th cells via delayed type hypersensitivity. [4].

Infection of the respiratory tract
HSV1 can cause disease in the respiratory tract on three different routes [5]:
1. reactivation of non replicating virus in the jugular portion of the vagus ganglion and migration to the lung epithelium on an unknown way.[6]
2. contiguous spread or aspiration [5, 7] of the virus from mucocutaneous lesions. This way of infection can cause tracheobronchial ulcers measuring 5 – 15 mm and to nodular and reticular hemorrhagic foci in the lung parenchyma around bronchi and bronchioles. [5],[8]  
3. hematogenous spread with evidence of HSV1 and HSV2 virus disseminated in several organs causing diffuse interstitial pneumonia [9] with random or military distributed hemorrhagic foci[8].

As 99% of primary HSV infections are inapparent[1], the host defense mechanisms must be insufficient to facilitate respiratory tract infection. Details of the emphasis of imbalance between pathogenic factors of the virus and the defense mechanisms of the host are still unknown. We know that despite the presence of antibodies the virus reactivates after local and/or systemic stimuli.

Local trauma, radiotherapy of the airways and squamous metaplasia (caused by smoking, chronic infection or the virus itself by disruption of the protective mucociliary function by its cytoytic effect) are local predisposing factors.

Malignancy[10], burns (50% of patients had HSV)[11, 12], radio-or chemotherapay, immunosuppressive therapy[13], organ transplantation[7], surgery [14] and prolonged mechanical ventilation[15] or ARDS are discussed as systemic predisposing factors to acquire pulmonary HSV-infection.[5, 16-18] Even nosocomial HSV- infections can rarely affect the respiratory tract [5, 14]

The clinical significance of Herpes simplex virus in the lower respiratory tract[19], the relation between colonization (presence of viral antigen – mostly by shedding from the upper respiratory tract) and infectious pulmonary disease caused by the virus is not exactly defined, because there is no specific clinical, radiological criterion and laboratory finding indicating disease.

In recent pro- and retrospective studies the presence of HSV1 in lower respiratory tract secretions was analyzed by viral culture [19, 20] or quantitative[20, 21] and/or qualitative[13] PCR and correlated to clinical, radiological and morphological pulmonary disease, but no standardized criteria for definition of pulmonary disease are established, so the pathogeneity of HSV for the lung is difficult to measure. It seems to be low. Out of 64 patients with HSV in bronchial aspirates or BAL one patient had severe lung injury and no other pathogens as possible cause for lung disease. In a review, analyzing 7 retrospective and 5 prospective studies Simoons-Smit finds incidences of HSV disease among HSV positive critically ill patients between 2 and 30 %. Criteria of manifestation of disease were: tracheobronchitis (3), pulmonary infiltrate (2), pneumonia (3), fever and lymphopenia (1), occult (1) and no criterion (2) For the author “the respiratory pathogenicity of HSV-1 in the critically-ill patient is at least doubtful.[5]. In a prospective study 2009, monitoring HSV in the lower respiratory tract of critically –ill patients by quantitative PCR, the authors found a frequency of 62% HSV in the LRT and an associated longer stay in the ICU and need of prolonged mechanical ventilation in those patients, but they could not quantify VAP incidence, nor the effect of antiviral therapy.[21]

Definitions of pulmonary disease:
Radiologically there are segmental and subsegmental ground glass opacities, scattered areas of consolidation. Pleural effusions are common. Those nonspecific signs are similar to mixed flora pneumonia [5, 22]
PaO2/FiO2 can be used to objective lung injury with values less than 200 mm Hg as indicator for severe lung injury.[19]

Measurement of protein permeability in the lungs can be expressed as the pulmonary leak index for gallium-67-labelled transferrin [23] as replacement of biopsies, and correlated to the virus load, measured by quantitative PCR in secretions as a possible marker of pathogeneity.
By bronchoscopy local edema, mucopurulent secretions and ulcers can be seen; biopsies from the margins of ulcerations, and secretion for cytological examination can be assessed.
Relatively specific histological respectively cytological findings in H&E or Giemsa stain are eosinophilic Cowdry A inclusion bodies, which are inactive aggregates of protein, e.g. recombinant genes emerging in a foreign microenvironment, especially in squamous epithelia. They can rarely be seen in pneumocytes. The infected cells can also reveal ground glass nuclei containing large amounts of basophilic inclusion material like Cowdry B- cells (CMV) and displaying marginated chromatin[9]

Immunohistochemically intracellular HSV 1 and HSV2 can specifically be detected in cells with and without inclusion bodies [11]. This method should be the gold standard for definition of HSV-associated pulmonary disease.
An indirect proof of pathogeneity is demonstration of treatment benefit [2]. It could be shown, that treatment with acyclovir can prevent shedding of virus, but no study could demonstrate a reduction of mortality.

Prevention and therapy
Preventive administration of acyclovir could not demonstrate a benefit[24], so treatment should be given to patients who are immunosuppressed including malignancy, burns and cytotoxic therapy, or if there is evidence of pulmonary parenchymal invasion or there is unexplained clinical deterioration. Immunocompetent critically ill
patients with herpetic mucosal infection and general signs of infection for focal or diffuse infiltrates on chest radiograph and no other causative microorganisms should also be treated without defined guidelines.

Conclusion:
Pathogenicity of HSV1 to the lungs in patients with solid tumors seems to be low, only rarely there are reports on life threatening HSV pneumonias. Suspicion of lower respiratory tract disease caused by HSV should initiate diagnostic efforts to proof the cytopathic effect of HSV. The morphology of the cytopathic effect of HSV in respiratory tract cells should be kept in mind for the distinction between infection and malignancy to direct therapy.

References