825 ORAL

Differences in the expression of epidermal growth factor receptor in lymph node metastases and primary tumors of the head and neck

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Purpose: An overexpression of the epidermal growth factor receptor (EGFR) has been found in a wide variety of malignancies including squamous cell carcinomas of the head and neck. The overexpression of EGFR is of increasing interest because of a possible contribution to metastasis. Primary tumors and metastasis may differ in the expression of EGFR and provide a basis for metastasis.

Methods: This study examined the expression of the cell-surface EGFR in frozen tissue samples from 30 primary carcinomas of the head and neck and from 30 lymph node metastases. The examination employed the use of an immunfluorescence assay using a mouse monoclonal antibody for localisation of immunoreactive EGFR.

Results: We saw a significant higher expression of EGFR in metastases than in primary tumors ($p = 0.005$). Examining the primaries, no correlation was seen between EGFR level and TNM-stage. We found an interesting correlation between EGFR level and histologic grading, immunoreactivity being significantly higher in G3 than in G1–G2 tumors ($p = 0.001$).

Conclusion: EGFR system may play an important role in the process of metastasis and elevated EGFR level might characterize more metastatic tumors. The significant correlation between EGFR level and the histologic grading suggests that EGFR expression may identify biologically more aggressive tumors.

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Oral squamous cell carcinoma (OSCC) – The role of to the tumor associated proteases uPA, PAI-1, cathepsin D, cathepsin B, cathepsin L and the receptor uPA-R

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Purpose: The pathway of plasmin activation is linked to tumor invasion and metastasis. The cascade of activation of cathepsin D, B, L and uPA, which is bound to its receptor uPA-R, induces plasmin which degregades the extracellular matrix and thus enables tumor invasion and metastasis. uPA is inactivated by PAI-I. Studies on various types of cancer proved the prognestic value of these proteases. Prospectively we determined the concentrations of uPA, uPA-R, PAI-1, cathepsin D, B and L.

Methods: From 220 patients with OSCC primary tumor- and benign tissue-specimen were taken. In these specimens (Triton X-100-extracts) concentrations of uPA, uPAR, PAI-1, cathepsins D, B and L were determined by ELISAs.

Results: Comparing intraindividually the concentration of proteases in malignant and benign tissue, in tumor specimen uPA-concentration was 20 times higher than in benign tissue, PAI-1 concentration was 6 times higher ($p < 0.0006$). Currently the measurements of uPAR, cathepsin D, cathepsin B and cathepsin L are evaluated.

Conclusion: The data indicates that uPA and PAI-1 could be of prognostic value in OSCC. In the next future the clinical and prognostic impact of these proteases for planning an individual oncological therapy has to be evaluated. The pathway of plasminogen activation could become a new strategy in the treatment of OSCC.

827 ORAL

Chromosomal alterations associated with malignancy in head and neck cancer

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Purpose: To discover molecular genetic alterations underlying the progression of head and neck squamous cell carcinomas (HNSCC) we performed Comparative Genomic Hybridization (CGH) on 50 primary tumors.

Methods: In CGH, equal amounts of differently labeled tumor DNA and normal reference DNA were hybridized simultaneously to normal metaphase chromosomes. They were visualized by different fluorochromes and the signal intensities were quantitated separately as gray levels along the single chromosomes. The over- and underrepresented DNA segments were determined by computation of ratio images and average ratio profiles.

Results: Prevalent changes observed in more than 50% of the HNSCC included deletions of chromosomes 1p, 4, 5q, 6q, 8p, 9p, 11, 13q, 18q and 21q and DNA overrepresentations of 11q13 as well as 3q, 8q, 16p, 17q, 19, 20q and 22q. The calculation of ratio profiles of tumor subgroups revealed that well differentiated carcinomas (G1) were defined by the deletions of chromosomes 3p, 5q and 9p together with the overrepresentation of 3q, suggesting the association with early tumor development. Accordingly, the undifferentiated tumors (G3) were characterized by additional deletions of chromosomes 4q, 8p, 11q, 13q, 18q, 21q and overrepresentations of 1p, 11q13, 19 and 22q.

Conclusion: Our data indicate that the CGH patterns of chromosomal imbalances may help to define the malignant potential of head and neck squamous cell carcinomas.

828 ORAL

Clinical and microbiological evaluation of radiotherapy (RT) induced mucositis in head and neck cancer patients

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Patients receiving curative radiotherapy (dose >66 Gy) were examined before, weekly during the course of RT and after RT. The extent of mucositis was recorded. Oropharyngeal bacterial flora was sampled before RT and regularly during the course using the oral rinse method. As mucositis prophylaxis patients used chlorhexidinegluconat 0.1% mouthrinse.

8.3% had cultures positive for yeast before RT, and 29.2% at the end of RT. 8 weeks after RT 33.3% were positive for yeast. Among patients who developed cultures positive for yeast at any time during the testperiod (62.5%), only 20% had received prior antibiotics. Before start of RT 20.8% had cultures positive for gram negative bacilli (GNB) increasing to 50.0% with positive cultures at the end of RT. 8 weeks after RT 33.3% had cultures positive for GNB. A total of 75% had cultures positive for GNB during the testperiod. Among these, 67% had received prior antibiotics.

Among the group of patients who developed cultures differing from normal flora during the first half of RT the median time to development of erythema grade 3 was 107 days compared to 43.5 days for patients with normal flora ($p = 0.07$). A trend towards earlier development of mucositis ($p = 0.103$ for grade 1 and $p = 0.232$ for grade 2) in patients with pathogenic cultures was found.

Conclusions: Among patients with cultures positive for GNB the majority had received prior antibiotics. Development of cultures positive for yeast was not associated with prior antibiotic therapy, and seems to be secondary to RT-induced mucositis. A possible correlation between toxicity of RT and pathogenic flora was detected.

829 ORAL

A comparative analysis between Ho's and UICC classification for nasopharyngeal carcinoma (NPC)

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Purpose: Ho's classification differs in some aspects of UICC staging: T1 Ho = T2&2 UICC; N category defines the level of nodal involvement (dimension for UICC); st V delineates hematogenous spread. The aim of the study is a comparison Ho v UICC classification.

Methods: Between 1987–95, 374 NPC pts were treated with radiotherapy (RT) (277 pts) or chemotherapy (BEC) followed by RT (97 pts), with no differences in survival (S) or disease free-survival (DFS). Kaplan-Meier method was used for actuarial S, DFS and freedom from distant metastasis (FDM) and log-rank method to test differences.

Results: 239 (64%) men, age 47 [8–78], histology (WHO): I v II v III: 76 v 36 v 262 pts. Stage distribution UICC/Ho: I 5/19, II 14/87, III 36/182, IV 319/80, V 0/6, shows an overcrowded st IV UICC versus (v) a well balanced Ho classification. *Overall S* (3y): st I v II v III v IV: 80% v 61% v 41% v 33% (Ho); I&II 80% v III 74% v IV 41% (UICC). *DFS:* st I v II v III v IV: 81% v 66% v 44% v 32% (Ho); I&II 81% v III 73% v IV 43% (UICC). There was a significant difference in S and DFS ($p < 0.01$) between Ho's stages in most comparisons (I v III, I v IV; II v III, II v IV). For UICC, only comparisons with

st IV were significant (I + II v IV, III v IV, $p < 0.02$). **FDM:** st I v II v III v IV: 100% v 84% v 76% v 51% pts (Ho): I + II v III v IV: 100% v 91% v 69% pts (UICC). Both classifications show a difference ($p < 0.01$) in the comparison with st IV (I v IV, II v IV, III v IV). For Ho, a difference st I v III ($p < 0.03$) was also found. The "N" category is the main factor which influences FDM in both classifications: N 0 v 1 v 2 v 3: 100% v 84% vs 68% vs 51% pts (Ho); 100% vs 84% vs 73% vs 53% pts (UICC). All comparisons between N categories were significant ($p < 0.01$) in Ho's classification, while N1 v N2 was not significant for UICC.

Conclusions: Ho's classification represents a useful complementary tool to UICC classification for NPC, because: 1) Ho's classification is more accurate in describing differences in S and DFS between st I, II v III. 2) N categories, as defined by Ho, demonstrate the prognostic role of the involved node level in the occurrence of distant metastases. 3) Distribution among different stages is better balanced for Ho classification.

830 POSTER

Comparative estimation of local control in radiotherapy supraglottic and glottic cancer

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Purpose: Comparative estimation of radiocurability in both groups of cancers localisated in upper and medium level of larynx.

Material and Methods: From 1985 to end 1989 544 patients with cancer of larynx were treated with primary radiotherapy. There were 388 patients with squamous cell supraglottic cancer and 156 patients with glottic cancer. The total dose was in range of 59–80 Gy.

Results: The 5-year local control in supraglottic cancer was 74% and 82% for glottic cancer. TCD for 50% probability, of local control (TCD_{50}) for supraglottic cancer were: 61.5 Gy (T_{1+2}), 66.5 Gy (T_3) and 69.5 Gy (T_4). There were lower TCD_{50} values for glottic cancer: 55.5 Gy (T_{1+2}), 63 Gy (T_3).

Conclusion: Higher radiocurability signes early glottic cancer T_{1+2} (TCD_{50} = 55.5 Gy) comparatively to supraglottic cancer T_{1+2} (TCD_{50} = 61.5 Gy). The same 50% probability of local control for T_3 glottic cancers is connected with Total Dose higher than in T_{1+2} of 7.5 Gy and for supraglottic cancer higher of 5.0 Gy. For the same 50% probability of local control supraglottic cancer T_{1+2} it is necessary to support Total Dose by about 6.0 Gy more than in glottic cancer T_{1+2} and in T_3 supraglottic cancer by about 5.0 Gy more than in glottic T_3 cancer.

831 POSTER

Is there any use in accelerated and hyperfractionated radiotherapy in locally advanced head and neck cancer?

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Purpose: In order to overcome accelerated tumor repopulation during radiotherapy a progressively accelerated hyperfractionated regimen was assessed for locally advanced head and neck cancer with initial poor prognostic factors.

Method: The treatment started with small field tumor volume with a conventional fractionation of 20 Gy in 10 fractions. This was followed by large fields by 1.66 Gy twice daily of 49.8 Gy for a total dose of 69.8 Gy. 104 patients with advanced head and neck cancer were treated. The oropharynx and larynx were the main localisations. The majority had stage III and IV tumors.

Results: After irradiation, a local control was obtained in 78/104 (75%) patients. Ten patients were salvaged with surgery after radiotherapy. During the observation period, 8 additional patients had a local relapse, thus the overall longterm control was 65%. Only 4 patients did not finish treatment because of severe acute toxicity.

Conclusions: The treatment schedule gives promising results. Shortening of treatment time certainly has its advantages. In discussing the results more emphasis will be given to a detailed analysis of early and late complications.

832 POSTER

Differential expression of mRNA in squamous cell carcinoma of the head and neck

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Purpose: Nowadays carcinogenesis is considered a multistage process involving many genetic alterations. Differential display is a recently developed technique that allows the detection of differentially expressed mRNA from different sources. The identification of differentially expressed genes in malignant cells may further elucidate the process of tumorigenesis.

Methods: RNA from oropharyngeal and laryngeal keratinocytes, and squamous cell carcinoma cells of the larynx and the hypopharynx was extracted and reverse transcibed. PCR was carried out with 26 arbitrary decamer primers and cDNA was separated electrophoretically. Differentially expressed bands were cloned and sequenced and a genebank search was carried out.

Results: Currently 7 differentially expressed DNA fragments in the squamous cell carcinoma cells were identified, cloned and sequenced. Four of these differentially expressed fragments did not show any homology with known human, animal, bacterial or viral gene sequences. The remaining three fragments did show a homology of up to 98% with known but not further characterized human gene sequences.

Conclusions: These differentially expressed genes or gene fragments may represent formerly unknown oncogenes and may help to better understand the multistep procedure of carcinogenesis in head and neck cancer.

833 POSTER

Sarcomas of the nasal cavity and paranasal sinuses

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Purpose: To analyse our experiences in treating nasal and paranasal sarcomas in adults, and to identify patterns of failure and prognostic factors.

Methods: 38 patients with Stage M0 disease treated by radiotherapy with or without surgery between 1960 and 1992 were analysed. Median follow up time was 71 months (range: 4–319 months). Local advanced tumors dominated: T1: 1, T2: 0, T3: 10, T4: 27 patients. Regional lymph node involvement was observed in 4 patients. Surgical excision was possible in 23 cases, but complete resection with negative surgical margins was achieved in only 6 cases.

Results: The calculated 5- and 10- year locoregional control-, cause specific survival- and disease free survival rates were 50%, 57%, 45%, and 50%, 48%, 45%, respectively. In case of combined therapy (surgery and radiotherapy) 5- and 10- year disease free survival rates were 69% and 51%, respectively. All patients with negative margins are under local control, 4 of them for over 13 years. In contrast we found poor results for patients with high-grade lesions and infiltration of the sinus sphenoidalis with 5- and 10- year locoregional control rates of 38%, 25% and 26%, 26%, respectively.

Conclusion: A combined treatment (surgery and radiotherapy), especially with radical surgical resection, should be the treatment of choice, because it offers the best chance for cure.

834 POSTER

Changes in tumor oxygenation in split course radiochemotherapy (RCTh)

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Purpose: The importance of oxygen as a modifying factor in radiation therapy was allready described by Gray in 1961, but clinical datas are still rare. Our study presents clinical datas about the oxygenation of tumors during RCTh (70 Gy, 5-FU, Mitomycin) and the influence of the oxygenation on the response of tumors.

Methods: Oxygen partial pressure (pO2) was measured in 32 patients with advanced carcinoma of head and neck using a pO2-histograph (Eppendorf, Germany). The clinical tumor response was quantified by measuring the tumor volume using ultrasonography. The time points of measurements were before RCTh, after first course of RCTh, after a two-week break of RCTh and at the end of RCTh.