weekly. Totally 46 patients were studied. The effective combination dose of Gefitinib + Eterocoxib was Gefitinib 500 mg and Eterocoxib 400 mg.
Recurrent and metastatic disease patients who were not candidates for definitive loco regional therapy and had received platinum based chemotherapy.
Results: Out of 46 patients − 40 were accessible patients. There were 18 patients in Methotrexate (Arm A) and 22 patients in the combination Arm of Gefitinib + Eterocoxib (Arm B). The Response rates, Time to Progression, Median Survival time in Arm A and Arm B are as follows:
Arm A − 1 partial response and 2 stable diseases (clinical benefit seen in 16.67%) with a median time of survival around 94 days, and time to progression 36 days.
Arm B − 1 complete response, 4 partial responses and 6 stable diseases (clinical benefit seen in 50%) with median time to progression 60 days, median survival time 165 days.
The treatment was relatively well tolerated with predictable toxicity including skin rash, diarrhea and dyspepsia. Exploratory study of quality of life showed improvement in quality of life in the experimental arm. Exploratory study of pharmaco-economics suggests that it is cost effective.
Conclusions: Gefitinib combined with Eterocoxib shows better response rates, Median Survival time and Quality of Life, than Methotrexate weekly and historical Gefitinib data. It is worthwhile to combine the 2 oral drugs for a disease status which does not have very effective treatment. A randomized Phase III trial can answer this question.

8590 POSTER

Concomitant Radiochemotherapy With Weekly Cisplatin and Daily Capecitabine in Locally Advanced Head and Neck Cancer-Safety and Efficacy

A. Lazescu[1], D. Stanculeanu[1], C. Georgescu[1], O. Toma[1], D. Zob[1], A. Cringeanu[1], D. Mitulescu[1], I. Stefanescu[1]. *[1]National Oncology Institute, Medical Oncology, Bucharest, Romania*

Loco-regionally advanced head and neck cancer is associated with a poor prognosis despite treatment with surgery or radiation or both. To improve the major end points of treatment we have focused on the used of concomitant radiochemotherapy. Cis and 5FU have been considered the standard for concomitant radiochemotherapy. The oral fluoropyrimidine, capecitabine was design to mimic continuous infusion 5FU. There is proved that oral capecitabine and 5FU continuous infusion have the same efficacy, therefore, our goal is to evaluate the efficacy and safety of concomitant chemoradiotherapy with cap and cis in locally advanced head and neck squamous cell carcinoma.
Method: Jan 2007–Jan 2009; 31 pts. with locally advanced head and neck squamous cell carcinoma, primary tumour sites: oral cavity − 6 pts, oropharynx − 10 pts, hypopharynx − 8 pts, nasopharynx − 6 pts, paranasal sinus − 1 pts, good performance status, good hepatic cardiac, renal and hematologic function.
Treatment: 70 Gy 3D-external beam RT (1.8−2 Gy/fr) concomitant with cap 660 mg/mp daily and cis 20 mg/mp weekly, entire period of RT.
Results: Follow up period − 2 years. CR − 24 pts. PR − 7 pts. PFS and OS rates at 2 years: 56% and 74% respectively. Toxicity grade 3−4 − neutropenia − 3 pts, digestive toxicity (vomiting, nausea) − 3 pts, mucositis − 5 pts. 4 pts needed to discontinuing the treatment due to toxicity. No death, no renal toxicity, no hand-foot sdr. were observed.
Conclusion: This modality of treatment was found to be well tolerated and effective in pts with locally advanced head and neck squamous cell carcinoma. This regimen can be regarded as an important chemoradiotherapy option for advanced head and neck squamous cell carcinoma and easily used in ambulatory patients. Long term follow-up is needed to evaluate (in larger trials) the late treatment failure and side effects.

8591 POSTER

Effects of Human Papillomavirus (HPV) and Other Potential Risk Factors on Survival in Patients With Oropharyngeal Cancer

M. Knoedler[1], A. Zakarneh[2], U. Zimmermann[3], K. Woelke[3], O. Kaschke[2], U. Keilholz[4]. *[1]Universitätsklinikum Benjamin Franklin, Med. Klinik III − Haematology & Oncology, Berlin, Germany; [2]St. Gertrauden Hospital, Department of Head and Neck Surgery, Berlin, Germany; [3]St. Gertrauden Hospital, Department of Pathology, Berlin, Germany; [4]Charité CBF, Department of Hematology and Oncology, Berlin, Germany*

Background: Oropharyngeal carcinomas are associated with HPV or with tobacco smoking and alcohol. HPV associated carcinomas arise most frequently in the tonsils and have a more favorable prognosis in contrast to tobacco smoking and alcohol induced carcinomas. Here we report on frequency and outcome of HPV associated oropharyngeal carcinomas (tonsils and base of tongue) in a Berlin cohort with high prevalence of smoking.
Methods: Between 2005 and 2009 114 patients with oropharyngeal squamous cell carcinomas were diagnosed in a city hospital, 60 arising from tonsils and 54 from the base of tongue. Patients received surgery, chemoradiation or radiotherapy according to stage of disease. Complete follow-up information was obtained in fall of 2010. Histologic slides were retrieved and stained for p16 as indicator of HPV associated disease. Proportional-hazard models and log-rank tests were used to compare the risk of progression and death among patient subgroups.
Results: Of all 114 patients, 81% were smokers and 64% tumours stained positive for p16 (tonsils 73%, base of tongue 54%). With a median follow-up of 28 months 31 patients had disease progression and 39 patients had died. 3-year PFS rates were 79% and 52% in patients with p16+ vs. p16- tumours ($p = 0.001$ by log-rank test) and 3-year OS rates were 78% and 39% in patients with p16+ vs. p16- tumours ($p < 0.001$ by log-rank test). In cox regression analysis, only stage and p16 were independant prognostic factors. For PFS p16 had a hazard ratio (HR) of 0.44% (95% CI, 0.25 to 0.78) and also for OS a HR of 0.44% (95% CI, 0.24 to 0.78).
Conclusions: Even in a European population with high prevalence of tobacco smoking, p16 positivity remains a strong favorable and independant risk factor, as has previously been shown in US cohorts with far lower smoking prevalence.

8592 POSTER

Long Term Quality of Life, Physical and Psychological Functioning in Patients Affected by Relapsed Head and Neck Cancer

M. Airoldi[1], M. Garzaro[2], L. Raimondo[2], G. Riva[2], O. Ostellino[1], G. Pecorari[2], C. Giordano[2]. *[1]San Giovanni Battista Hospital, 2nd Medical Oncology Division, Turin, Italy; [2]University of Turin, Clinical Physiopathology Department, Turin, Italy*

Background: Primary head and neck squamous cell carcinomas (HNSCC) and their recurrences can heavily affect patient's quality of life (QoL). Aim of our study was the evaluation of the impact of treatment on QoL, physical and psychological functioning of patients affected by recurrent HNSCC.
Material and Methods: The sample was composed by 34 patients affected by recurrent HNSCC. Primary tumour treatment was as follows: exclusive RT (radiotherapy) 18%, S+RT 55%, RT + chemotherapy (CT) 27%. In order to evaluate the late effects of RT we used the RTOG–EORTC late radiation morbidity score plus the DISCHE morbidity recording scheme.
Psycho-oncological assessment included: HADS, MADRS, MINI MAC, EORTC QoL HN 35.
Results: Among this population, 55% of pts relapsed on T, 15% on N, 21% on T+N and 9% on M. Recurrences were treated with S+CT 6%, RT+CT 21% and CT alone 73%. The late toxicity evaluation demonstrates that skin alterations, salivary glands impairement, subcutaneous fibrosis and mucous membrane alterations are the most relevant and severe damages. After a median follow-up of 60±26 months, analysing RTOG-EORTC scale, high scores of skin and mucous membrane alterations are related ($p < 0.05$) with higher levels of anxiety and depression, negative coping styles (reduction of fighting spirit, anxiety and depression) are increased by salivary and mucous membrane dysfunctions ($p < 0.05$), moreover lower levels of QoL, in particular physical and social functioning, are correlated with higher levels of mucous membrane damages ($p < 0.05$); all the mentioned above symptoms increase negative thoughts ($p < 0.05$). DISCHE findings are superimposeable.
Conclusions- Treatment of relapsed HNSCC added to surgery and or RT and or CHT on the primary tumour could result in a heavy addictive effect on mucous membrane, skin, subcutaneous tissues and salivary glands referred symptoms. Negative coping styles and thoughts, increased anxiety and depression and lower levels of QoL are strongly associated to high scores of such symptoms.

8593 POSTER

VEGF and Oral Cancer − ex Vivo and in Vitro Studies

M. Islam[1], H. Alkhadar[1], Z. Paterson[1], M. Macluskey[1], S. Jones[1], P. Mossey[1], I. Ellis[1]. *[1]University of Dundee, The Dental School, Dundee, United Kingdom*

Introduction: Scotland has the highest occurrence of oral cancers in both men and women across the UK (CR-UK, 2006) and the incidence is on the rise. The frequency in Scottish males is 18.4 per 100,000 (UK average is 11.9) and in Scottish women is 7.4 per 100,000 (UK average is 5.8). The aim of this study was to investigate the VEGF family as markers of tumour progression and to investigate how VEGF affects cell migration and signalling pathways, in vitro.
Materials and Methods: Tissue was collected from a cohort of 64 patients with oral cancer and 22 patients with dysplastic lesions. The tissue was analysed for expression of VEGF-A and VEGF-C by immunohistochemistry and then semi-quantitatively assessed. A cohort of serum samples was

also taken from the same 63 HNSCC patients, 8 dysplasia patients and 29 controls. Pre-treatment serum levels of the following markers were determined; VEGF-A, VEGF-C, VEGF-D and VEGFR1 using commercially available immunoassays. Using a normal oral stromal fibroblast line and a tumour oral epithelial cell line, we investigated the effect of recombinant $VEGF_{121}$ on cell migration in the Boyden chamber. We investigated the effect of recombinant $VEGF_{121}$ on the same cell lines using Western blotting with phospho-specific antibodies to Akt residues Thr308 and Ser473.
Results: The resultant data indicated that both VEGF-A and VEGF-C expression were significantly elevated in cancer patients compared to dysplastic patients. The mean concentrations of VEGF-A, -C, -D and VEGFR1 were higher in HNSCC in comparison to normal ($p = 0.07$; $p = 0.001$; $p = 0.0001$, $p = 0.001$ respectively). The tumour cells were stimulated to migrate through the pores of the filter by VEGF. Cell migration displayed a dose response effect with maximal stimulation at approximately 10 ng/ml VEGF. An inhibitor of PI3 kinase, LY294002, reduced VEGF stimulated migration to baseline levels. The normal fibroblasts, in comparison, were not stimulated to migrate. Akt is activated in some tumours and is a downstream effector molecule in a number of tyrosine kinase receptor pathways. The oral cancer cells exhibited a linear decrease in Akt phosphorylation at Thr308 with increasing VEGF concentration. In contrast, the normal fibroblasts displayed an increase in Akt phosphorylation at Thr308 with increasing VEGF concentration. Phosphorylation of Akt at Ser473 was increased in both cell lines, the degree of phosphorylation being dependent upon VEGF concentration.
Conclusion: The data we have collected increases the knowledge and understanding of oral cancer progression and its possible underlying molecular mechanisms. VEGF expression is increased in our patients with oral cancer and in vitro, the motility of cancer cells is increased by VEGF and can be blocked by inhibitors of the PI3-kinase pathway. This has important implications to tumour angiogenesis, lymphangiogenesis and metastasis. A study using other PI3 kinase/Akt pathway inhibitors may be transferrable to clinical practice in the future.

8594 POSTER

Gene Copy Number as Predictive Marker for Cetuximab Resistance in Head and Neck Squamous Cell Carcinomas

F. Jerhammar[1], J. Welander[2], A.C. Johansson[1], P. Soderkvist[2], K. Roberg[3]. *[1]Linkoping University, Division of Otorhinolaryngology, Linkoping, Sweden; [2]Linkoping University, Division of Cell Biology, Linkoping, Sweden; [3]Linkoping University Hospital, Division of Otorhinolaryngology, Linkoping, Sweden*

Background: Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR). It has proven a sufficient treatment in combination with radiotherapy in head and neck squamous cell carcinoma (HNSCC). However, far from all patients benefit from this therapy and predictive biomarkers of response to cetuximab are therefore required.
Materials and Methods: We evaluated the intrinsic cetuximab sensitivity (ICeS) in 35 HNSCC cell lines (established by Professor Grénman, University of Turku, Finland) by a crystal violet assay, and results were expressed as survival compared to control cells. EGFR expression was measured with an ELISA assay and correlation analysis was performed. Five resistant and five sensitive cell lines were selected for gene copy number analysis on Affymetrix SNP 6.0 chips. Single genes representing amplified regions will be verified by quantitative real time PCR (qPCR).
Results: The mean ICeS was 0.76, and the variation was between 0.16 and 1.4. Cell lines with survival exceeding 0.95 were considered resistant, and survival below 0.5 regarded as sensitive. Interestingly, two cell lines proliferated significantly under cetuximab treatment. Twelve cell lines (34%) were resistant to cetuximab, whereas five (14%) were sensitive. The EGFR expression varied greatly among the cell lines. However, there was no correlation between cetuximab sensitivity (ICeS) and EGFR expression ($r^2 = 0.11$). A total of 51 genes were amplified in resistant cells and not in sensitive cells. They were all distributed on two genomic regions, 11q22 and 5p13−15.
Conclusions: Our results show a great divergence in the cellular response to cetuximab treatment. Since the expression of the receptor itself is not an adequate predictive marker, other factors must be uncovered. Chromosome regions 11q22 and 5p13−15 are amplified in Cetuximab resistant cells. Possible driver genes are being evaluated at present.

8595 POSTER

MicroRNA Signature and Functional Characterization of miR-10b in Oral Cancer

A. Cheng[1], Y.C. Lu[1], Y.J. Chen[1], J. Chang[2]. *[1]Chang Gung University, Department of Medical Biotechnology, Taoyuan, Taiwan; [2]Chang Gung Memorial Hospital, Department of Radiation Oncology, Taoyuan, Taiwan*

MicroRNA (miRNA) participates in a variety of biological processes, and dysregulation of miRNA is associated with malignant transformation. In this study, we determined specific profile of miRNA associated with oral cancer. Using miRNA array screening method, 23 miRNA were found considerably differential expressions between 6 oral cancer cell lines and 5 lines of normal oral keratinocytes. In which, 10 miRNAs showed the highest significant difference after independent examination by RT-qPCR. Eight molecules were up-regulated; miR-10b, miR-196a, miR-198b, miR-582−5p, miR-15b, miR-301, miR-148b, and miR-128a; and 2 molecules-miR-503 and miR-31 were down-regulated. The miR-10b was further examined, and its functions were characterized in two oral cancer cell lines. The miR-10b actively promotes cell migration (2.6- to 3.6-fold) and invasion (1.7- to 1.9-fold), but has no effect on cell growth or chemo-/radiosensitivity. Furthermore, plasma miR-10b was considerably elevated (20-fold) post-tumour formation in the xenografted mice, suggesting potential application of this molecule in cancer detection.
In conclusion, we have identified at least 10 miRNAs significantly associated with oral cancer, with low *P* values and high differential expressions. The miR-10b actively participates in cancer formation through promoting cell migration and invasion. There study provides knowledge base for future clinical application of microRNA in oral cancer.

8596 POSTER

Long Standing Goitres Resulting in Malignancies

N. Singh[1], H. Chandra[1]. *[1]Forrd Hospital & Research Center, General & Endocrine Surgery, Lucknow, India*

Background: To evaluate malignancy rates in long standing goitres.
Material and Methods: Retrospective study of 73 patients with long standing goiters, more than 5 yrs duration, who underwent surgical procedures in our department.
Results: There were 28 males and 45 females. The symptoms ranged from 5 yrs to 30 yrs (mean 13.05 yrs). Twenty-one patients (29%) had histologically proven carcinoma of the thyroid. Malignancy was found in 9 females and 12 males. There were 9 patients with papillary carcinoma, 5 with follicular carcinoma, 6 anaplastic and one with medullary carcinoma. The mean duration of symptoms in patients with maligancies was 13.09 yrs as compared to 12.1 yrs in patients with benign thyroid disease.
Conclusion: Long standing goitres have a high chance of becoming malignant, especially in males.

8597 POSTER

Triple Tracer Molecular Imaging in Advanced Head and Neck Cancer

J. Kazmierska[1], W. Cholewinski[2], T. Piotrowski[3], A. Ryczkowski[3]. *[1]Greater Poland Cancer Centre, Radiotherapy Department II, Poznan, Poland; [2]Greater Poland Cancer Centre, Nuclear Medicine Department, Poznan, Poland; [3]Greater Poland Cancer Centre, Medical Physics Department, Poznan, Poland*

Background: Despite progress in treatment of advanced head and neck cancer, cure rate remains unsatisfactory. Assessment of both morphological and molecular characteristics of the tumour would allow optimizing the treatment in the future.
Aim of the study is an assessment of proliferation, glucose metabolism and hypoxia in inoperable, advanced head and neck tumours before and during radical chemoradiotherapy.
Materials and Methods: Between July 2010 and March 2011, 17 patients were included into the study: 9 oropharynx, 3 oral cavity, 3 larynx 2 hypopharynx. All patients were treated by radical chemoradiotherapy, consisting of 70 Gy in 35 fractions and concurrent cisplatin administration: 100 mg/m^2 on days 1, 22, 43. PET/CT with fluorodeoxyglucose (FDG), fluorotymidyne (FLT) and fluoromisonidazole (FMISO) was performed in week preceding start of the treatment. FLT PET was repeated twice during treatment, after 14 Gy and 28 Gy, FMISO was repeated once, after 36 Gy. Primary tumours were manually delineated on contrast CT scans obtained for radiotherapy treatment planning and then automatically on PET scans, using gradient based method. Volumes delineated and standardized uptake values (SUV) were analyzed, and differences were calculated using Wilcoxon Matched Paired Test.
Results: 70 PET/CT images were analysed. Correlation was found between primary tumour volumes delineated on CT scans and FDG and