

## Abstracts of the Second European Conference on Head and Neck Cancer, Lille, October 16–18, 2003 and the foundation of the European Head and Neck Society (EHNS)

In 2000 a discussion was initiated about the opportunity of a European Head and Neck Society. Already at that time, the British, the Dutch and the Scandinavian Head and Neck Societies had planned to meet together in Lille, France.

In order to assess the feasibility of such a European venture it was decided to change the three societies' meeting into the First European Conference on Head and Neck Cancer, which was held in Lille 2001. This meeting was considered a success both concerning content and the attendance of representatives from 19 different European countries. During the business meeting a consensus rose on the need of a multidisciplinary European Head and Neck Society.

The goals of this multidisciplinary European Head and Neck Society (EHNS) will be to promote exchange of knowledge in all aspects of Head and Neck neoplastic diseases and to promote the highest standards of research, education, training, disease prevention and patient care.

During the Second European Conference on Head and Neck Cancer in Lille 2003 it was decided to establish a European Head and Neck Society. For the first four years, 2003 to 2007 the Founding Board will consist of the Organizing Committee of the two first European conferences. Advisors will be co-opted from the corresponding European Societies to ensure the multidisciplinary format of the EHNS. Before the Third European Conference to be held in 2007 a call for candidatures will be organized.

### Organizing Committee:

Guy Andry (B)

Dominique Chevalier (F)

Newell Johnson (UK)

Rene Leemans (NL)

Jean Louis Lefebvre (F)

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### Importance of biomarkers to predict the individual cancer risk in the Upper Aerodigestivtract

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**Background:** A couple of valid biomarkers may help in future to identify persons with an increased cancer risk. Basing on the concept of field cancerisation first described by Slaughter in 1953, early malignant changes in healthy mucosa of the oral cavity were detected. The aim of our study was to evaluate different biomarkers to develop a secondary prevention concept to estimate the individual cancer risk in endangered persons (tobacco- and alcohol abuse). The possibilities of exfoliative cytology and of toxicologic investigations of saliva were analysed.

**Methods:** In three different studies including 100 patients with carcinomas of the upper aerodigestive tract and 331 healthy probands brush cytologies of morphological healthy buccal mucosa were analyzed using the micronucleus assay and immunocytochemical markers (MIB 1, PCNA, p 53, cyclin D 1). Gen- and cytotoxicity activities of saliva were measured using the Ames – test and the Plating efficiency – test.

**Results:** The micronucleus test and the quantitative analysis of immunocytochemical markers clearly confirmed the phenomenon of field cancerization in the upper aerodigestive tract. The relative risk of a tumor disease in the group of smokers with a defined micronucleus frequency was estimated (OR= 8.04) ( $p < 0.0001$ ) and a high risk group was identified. A cytotoxic activity (plating efficiency) appeared at 5% of the saliva specimen of all study participants. The saliva of smokers showed a significantly higher cytotoxicity than that of non-smokers ( $p < 0.002$ ). Strong cytotoxic sam-

ples (7/36) could only be verified from smokers and tumor patients. A six times higher genotoxic activity of saliva was measured in the Ames – test (OR=6.0;  $p = 0.008$ ) in the group of smokers with regular alcohol abuse compared to the non-abusers.

**Conclusions:** A combination of valid biomarkers may help to detect persons with an increased cancer risk in the upper aerodigestive tract and it seems possible to estimate the individual cancer risk. The hypothesis of a field change by Slaughter is confirmed by the micronucleus assay and immunocytology.

**Key words:** biomarker, cancer risk

### HPV and risk of oral/oropharyngeal cancer in the Czech Republic

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**Background:** Human papillomaviruses (HPV) are the main etiological factor of cervical carcinoma (CC) and its precancerous lesions development but HPV are also considered as a possible etiological factor of the intraepithelial neoplasias and cancers of vulva, vagina, penis, perianal and anal region. HPVs have been detected in 100% of the recurrent laryngeal papillomatosis lesions and in about 20% of malignant diseases of the head and neck. Since it is expected that a vaccination for HPV will be developed in near future, it is crucial to examine the etiological relationship between HPV infection and a wide spectrum of malignant diseases.

**Methods:** Patients with oral/oropharyngeal carcinoma visiting the Dept. of Otolaryngology Head and Neck Surgery, Prague in the

period of 2001-2003 and frequency age matched controls have been enrolled in our study. All patients signed the information consent and filled up a detailed risk factor questionnaire. From each subject oral lavage and blood was taken. A tissue from all patients treated surgically was analyzed histologically. HPV DNA detection was done by means of polymerase chain reaction (PCR) with general GP5+/GP6+ primers in DNA extracted from oral rinse cells and from a paraffin embedded tumor tissues. The detection of HPV specific antibodies was accessed by ELISA with VLPs specific for HPV 6, 11, 16, 18, 31 and 33.

**Results:** Up today, 67 patients have been enrolled in our study. 11 patients had oral cancer and 56 patients had cancer of oropharynx. HPV DNA had been detected in 62% of tumour samples. The most prevalent was HPV type 16 (62%); 38% of samples were positive for more than one HPV type.

**Conclusions:** Based on our preliminary data we suggest that HPVs are prevalent in the oral and oropharyngeal malignant lesions and the heterogeneity of HPV types is extensive. We hypothesized that the high prevalence of HPV DNA in our study could be the result of specific lifestyle and/or environmental risk factors.

### Is there interindividual variation in susceptibility to laryngeal cancer?

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**Background:** Tobacco- and to a lesser degree alcohol consumption as well as some occupational factors are recognised risk factors for laryngeal carcinoma, however individual susceptibility to these environmental factors varies.

**Aims:** We investigated the potential risk-modifying effect of genetic polymorphisms in enzymes involved in ethanol and tobacco carcinogen metabolism and factors influencing individual mutagen sensitivity, like activity of poly(ADP-ribose)polymerase (PARP) for laryngeal cancer.

**Methods:** In the period from 1998 to 2000, 257 cases suffering from laryngeal carcinoma and 769 population-based controls, matched by age and gender, were examined by a specific questionnaire for environmental and occupational risk factors. In a subgroup blood was taken from 245 cases and 251 controls for genotyping of genetic polymorphisms in ADH1B, ADH1C, GSTM1 and GSTT1, using genomic DNA isolated from peripheral lymphocytes and employing PCR and PCR/RFLP based methods [1]. PARP activity was assessed as bleomycin -induced poly(ADP-ribose) (PAR) formation in human peripheral blood lymphocytes by quantitative immunofluorescence analysis from 69 cases and 125 controls [2].

**Results:** Multiple logistic regression analyses were carried out to determine the gene-environment interaction in relation to laryngeal cancer risk. Peripheral blood lymphocytes from laryngeal cancer patients showed significantly less damage-induced poly(ADP-ribose) formation. However, none of the investigated genetic polymorphisms markedly modified the laryngeal cancer risk, even after stratification by alcohol consumption or cumulative smoking exposure.

**Conclusions:** Our results suggest that a reduced capacity of somatic cells to synthesize PAR might be associated with an increased risk for laryngeal cancer. Individual susceptibility might play a role in laryngeal cancer risk but the biological determinants are still not fully understood.

1) Pharmacogenetics 2003;13(4):225-230.

2) Int J Cancer. 2002; 98(5):780-4.

### Integration of genomic HPV 16 DNA is associated with p16<sup>INK4a</sup> overexpression in tonsillar carcinomas

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**Background:** In a previous fluorescence in situ hybridization (FISH) study, we observed human papillomavirus (HPV) type 16

DNA integration in the tumor cell genome in 21% of head and neck squamous cell carcinomas, particularly in tonsillar carcinomas. Because also no p53 mutations in exons 5-8 were detected, this subset of tumors may comprise a distinct pathological entity. In order to further substantiate this hypothesis, we analyzed p16<sup>INK4A</sup> expression in 81 tonsillar carcinomas, because p16<sup>INK4A</sup> has been reported to be a specific marker for oncogenic HPV-containing (pre)neo-plastic lesions of the uterine cervix. p16<sup>INK4A</sup> expression, clinical data as well as tobacco and alcohol consumption of patients were correlated with HPV status.

**Methods:** Tissue sections of paraffin-embedded tonsillar carcinomas were subjected to FISH using a HPV 16-specific DNA probe to assess the frequency of tumors exhibiting HPV integration. Subsequent sections were used for immunohistochemical assessment of p16<sup>INK4A</sup> overexpression. Clinical data and alcohol and tobacco exposures of patients were obtained from medical records.

**Results:** FISH detected HPV 16 integration in 33 of 81 (41%) carcinomas, 32 of which also harbored diffuse p16<sup>INK4A</sup> immunostaining. In contrast, only 5 of 48 HPV-negative carcinomas did stain for p16<sup>INK4A</sup>. Thus, a very strong correlation was found between p16<sup>INK4A</sup> overexpression and HPV-containing tonsillar carcinomas ( $P < 0.0001$ ). Furthermore, a significant, inverse relation was found between the presence of HPV in the tumor and tobacco and/or alcohol consumption ( $P \leq 0.0104$ ). HPV-positive carcinomas also showed to be often smaller ( $\leq 4$  cm) and less well differentiated than HPV-negative tumors ( $P = 0.0236$  and  $0.009$ , respectively).

**Conclusions:** Our results indicate a remarkable correlation between HPV 16 integration and p16<sup>INK4A</sup> overexpression in tonsillar carcinomas, resembling the situation for (pre)invasive lesions of the uterine cervix. This suggests that p16<sup>INK4A</sup> may be considered as an alternative biomarker for HPV detection. Together with the strongly reduced or absent exposure to tobacco and alcohol in these patients, our study provides further evidence for HPV-positive tonsillar carcinomas representing a different tumor entity.

### Immunologic aspects in patients with head & neck carcinoma

HJ. Aarstad, J. Olofsson, JH. Heimdal (Bergen, Norway)

**Background:** Despite seemingly improvements in treatment of HNSCC no major progress in patient life expectancy has been encountered. A basis for immunologic intervention may be found in the mononuclear phagocyte system. Human monocytes may selectively bind to tumour cells. IFN- $\gamma$ -stimulated monocytes have been shown to act cytotoxic towards human allogeneous tumours. Monocytes have potential for recruiting/stimulating T-lymphocytes and natural killer (NK) cells.

**Methods:** Patients with recently diagnosed HNSCC were included, all males, below 80 years of age and with no immuno-active disease or medication. A method was adopted by which PBMC were isolated by gradient centrifugation and monocytes separated from PBMC population by adherence to plastic wells in vitro. Autologous serum was used as serum source in culture media in order to get better in vivo similarity. We have used a tissue culture technique which is to form in vitro fragment spheroids.

**Results:** Monocytes in HNSCC patients stimulated with LPS secreted increased amount of IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , but not IL-12. This is a sign of monocyte priming in the HNSCC patient. A reduced co-culture response was shown when a semi-permeable membrane separated the monocytes and F-spheroids. A diminished co-culture response follows the addition of mannose. The observation of our studies indicates that monocytes, when activated in co-culture regulate IL-6 and TNF- $\alpha$  production separately - pretranscriptionally.

**Conclusions:** The present work has determined that monocytes are activated by contact with HNSCC cells. This may form the basis of therapy based on monocyte priming.

### Immunological effects of intratumoral rhIL-12 administered in head and neck squamous cell carcinoma (HNSCC) patients

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**Background:** HNSCC patients have both a local and a generalised immunosuppression. IL-12 promotes the Thelper 1 response and activates and induces a proliferation of cytotoxic T cells and natural killer (NK) cells.

**Methods:** We have performed 2 clinical studies in HNSCC patients with i.t (rhIL-12). In the 1st study (phase Ib) the primary objective was to assess the toxicity of i.t. administration of rhIL-12, 6 recurrent HNSCC patients, who had surgery and radiotherapy before. In the 2nd study (phase Ib-II) the primary objective was to investigate the immunological effects of IL-12, in 10 non-pre-treated HNSCC patients. rhIL-12 was injected i.t. in the wait before the surgery. In both studies rhIL-12 was administered at two dose levels: 100 and 300ng/kg, once a week. The mean number of administered injections was 9 (3-24) in the 1st and 2 (1-3) in the 2nd study.

**Results:** In the 2nd study the toxicity was more pronounced than in the 1st study, probably due a better immune competence in non pre-treated HNSCC patients. In the 2nd study more and larger lymph nodes were detected in the IL-12 treated versus control patients. Results of flowcytometric analysis of lymphocyte subsets, real-time semi-quantitative PCR analysis of cytokines, Thelper 1 and Thelper 2 transcriptionfactors and immunohistochemistry of immune cells (e.g. dendritic cells) will be presented.

**Conclusions:** rhIL-12 at these dose levels and schedule resulted in measurable immunological responses.

### HNSCC spheroids monokine secretion and autologous monocyte co-culture activation versus tnm stage, inflammatory state and macrophage density

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**Background:** Fragment (F)-spheroids from head and neck squamous cell carcinoma patients stimulate autologous monocytes in vitro to secrete IL-6 and MCP-1 when co-cultured.

**Methods:** The density of epithelial, fibroblasts and macrophages was determined in F-spheroids and tumor tissue. The TNM stage, the donor inflammatory state, the F-spheroid macrophage density as well as the F-spheroid IL-6, MCP-1 and TNF- $\alpha$  secretion and co-culture responses were analyzed. After treated with the monocyte killing substance L-Leucine Methyl ester (LLME) the fresh cut tumor tissue grew into F-spheroids and was examined for IL-6 production.

**Results:** The percentage of epithelial cells decreased during spheroid formation. There was an inverse relation between the erythrocyte sedimentation rate at monocyte harvest and the MCP-1 co-culture response ( $\tau=0.48$ ,  $p<0.01$ ). There was a higher secretion of MCP-1 in malignant F-spheroids compared to the benign. None of the F-spheroids secreted TNF- $\alpha$ . Monocytes secreted more IL-6 when co-cultured with malignant compared to co-culture with benign F-spheroids. The IL-6 response in co-culture of malignant F-spheroids correlated with macrophage density in malignant F-spheroids ( $\tau=0.39$ ,  $p<0.05$ ). N-stage correlated with spheroid IL-6 secretion rate ( $\tau=0.56$ ,  $p<0.05$ ). A correlation was observed between malignant and benign F-spheroid co-culture IL-6 ( $\tau=0.46$ ,  $p<0.05$ ) and MCP-1 ( $\tau=0.43$ ,  $p<0.05$ ) responses. Furthermore we found a correlation between malignant F-spheroid MCP-1 secretion and the co-culture IL-6 response ( $\tau=0.44$ ,  $p<0.05$ ) as well as between benign and malignant spheroid MCP-1 secretion ( $\tau=0.67$ ,  $p<0.01$ ). We will also present a significant reduction in the production of IL-6 from the F-spheroid when treated with LLME.

**Conclusions:** Tumor associated macrophages play an important role in the production of IL-6 from the F-spheroid. Monocyte co-culture response and monokine secretion from the spheroids seem to relate to prognosis, inflammatory state and to each other. MCP-1 secretion was associated with the functional status of the mono-

cyte, while the IL-6 response in co-culture was associated with the disease state.

### Differential expression and cytogenetic aberration profiles of tumor suppressor- and oncogene pathways in Head and Neck cancers

#### revealed by tissue microarray analysis

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**Background:** Head and neck squamous cell carcinomas (HNSCC) are very heterogeneous in their biological and clinical behavior. The aim of this study was to propose a tumor classification into groups with homogeneous biological and clinical characteristics.

**Methods:** Tissue microarrays containing a total of 600 HNSCC were used to analyse the expression of proteins with major roles in control of the cell cycle, apoptosis, cytoskeletal architecture and cell adhesion by immunohistochemistry, including tyramide signal amplification. Gene copy number gains and losses were studied by FISH.

**Results:** The relationship between reduced pRb and increased p16<sup>INK4a</sup> expression which was previously established in both HNSCC and cervical cancer, could be fully confirmed ( $p<0.0001$ ), illustrating the feasibility and usefulness of the tissue microarrays. In addition, the pRb-defective, HPV oncogene expressing HNSCC showed an increased prevalence of reduced cyokeratin14 expression. This indicates disruption of cytoskeletal architecture in these tumors, in agreement with their poorer histology. We found significant differences between the different anatomical tumor sites both in expression profiles as well as in cytogenetic alterations.

**Conclusions:** Our data demonstrate that different pathogenetic pathways drive the carcinogenetic process in the different sites and contribute to the differential clinical behavior. Molecular classification employing tissue microarrays will eventually lead to a better tumor classification into groups with more homogeneous biological and clinical behavior.

### Second field tumors in oral and oropharyngeal cancer: molecular techniques provide new insights and definitions

T. Maarten, RH. Brakenhoff, CR. Leemans, BJM. Braakhuis (Amsterdam, The Netherlands)

**Background:** Second primary tumors (SPT) and local recurrences (LR) are a significant problem in head and neck squamous cell carcinomas (HNSCC). Thus far, the definitions of SPT and LR are based on clinical parameters: location and time interval.

**Methods:** Our recent molecular studies have provided new insight in HNSCC carcinogenesis leading to a better understanding of how of SPT and LR develop.

**Results:** A crucial step is the outgrowth of a preneoplastic field of genetically altered cells that precedes HNSCC development. This field has a monoclonal origin and clonal divergence takes place during progression and eventually one subclone develops into carcinoma. The population of genetically altered cells have a high proliferative capacity (as measured by Ki-67 positivity), indicating that fields expand and thereby replace the normal mucosal epithelium. Moreover, fields are shown to be very large (over 7 cm in diameter) and are usually not detected by routine diagnostic techniques. An important clinical consequence is that fields often remain after surgery and may give rise to (genetically related) new tumors. We have provided convincing evidence for the development of these new tumors and have designated these new tumors: second field tumors (SFT). Considering the etiological differences, we believe it is important to define in molecular terms and discriminate an SFT, a "true SPT", and a "true LR".

**Conclusions:** The development of an expanding preneoplastic field is a critical step in HNSCC development with important clinical consequences. Diagnosis and treatment of HNSCC should not be focused on the tumor only, but also on the field it developed from.

### **p53 polymorphism predicts outcome in advanced head and neck cancer.**

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**Background:** The effect of p53 on clinical outcome in head and neck cancer (HNC) remains unclear. A polymorphism at codon 72 of p53 encodes either arginine (R) or proline (P). Mutations in 72R are more frequent in cancer and some 72R p53 mutants inhibit the pro-apoptotic protein p53. The aim of this study was to address the significance of p53 polymorphism, we analysed p53 mutation and polymorphism in 70 advanced HNC patients and sought correlations with clinical outcome.

**Methods:** Patients received chemo-radiotherapy. DNA was isolated from paraffin sections and the entire coding sequence of p53 was determined.

**Results:** Mutations occurred in 40/70 cases and, in germ-line 72 R/P heterozygotes, were significantly more common in 72R ( $p=0.0394$ ). 93% of cases without mutations gained complete response (CR) to treatment versus 58% of cases with mutations ( $p=0.0044$ ). At a median follow up of 33.9 months, progression-free survival (PFS) was significantly longer for cases without than with mutation (% progression-free at 2 years 82% versus 46%,  $p<0.0007$ ) and, for the 40 cases with mutation, if the mutant allele was 72P rather than 72R (% progression free at 2 years 83% vs 38%,  $p=0.0087$ ). Survival was significantly longer for cases lacking p53 mutation (% surviving at 2 years 82% vs 62%,  $p=0.0058$ ) and, for the 40 cases with mutation, if the mutant allele was 72P (% surviving at 2 years 100% versus 53%,  $p=0.0044$ ).

**Conclusions:** p53 mutations in 72R are associated with worse clinical outcome in HNC. Future studies of p53 should consider polymorphism in addition to mutations.

### **The prognostic value of CYFRA 21-1, a new tumour marker, in squamous cell carcinoma of the upper aero-digestive tract.**

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**Background:** The aim of this prospective study is to determine whether the pre-treatment serum concentrations of Cyfra 21-1, a new tumour marker, have a prognostic value in squamous cell carcinoma of the upper aero-digestive tract (UADT).

**Methods:** Serum concentrations prior to therapy of Cyfra 21-1 are measured in a group of 300 patients, not previously treated, presenting squamous cell carcinoma of the UADT. These concentrations are compared with the size of the tumour, size of the lymph nodes, presence of metastases and stage of the disease. The evolution of the overall survival and disease free survival is compared in relation to the pre-treatment serum concentrations of Cyfra 21-1. Finally, the concentrations of Cyfra 21-1 are compared, by a Cox model, with the classical prognostic factors of carcinomas of the UADT (TNM, stage of the disease, age and sex) to determine whether Cyfra 21-1 is an independent prognostic factor.

**Results:** Serum concentrations of Cyfra 21-1 are all the higher as the tumour mass is substantial, and they are statistically correlated with the T, the N, the M as well as the stage of the disease. The overall survival and disease free survival are not as good in patients with high serum concentrations, and these differences are statistically significant ( $p<0.001$ ). The Cox model allows us to conclude that Cyfra 21-1 is a prognostic marker which is independent from other classical prognostic factors.

**Conclusions:** Cyfra 21-1 is an interesting tumour marker whose use could be proposed routinely for the monitoring of squamous cell carcinomas of the UADT. The pre-treatment serum concentrations are correlated with the tumour mass, and Cyfra 21-1 can be considered as an independent prognostic marker. High concentrations are a sign that distant metastases must be searched for, and that a poor overall survival and disease free survival must be expected.

### **Exogenous and endogenous markers of hypoxia as predictors of outcome in head and neck cancer**

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**Background:** Hypoxia is associated with tumor aggressiveness and an important cause of resistance to radiation treatment. Assays of tumor hypoxia could provide selection tools for hypoxia modifying treatments. The aim of this study was to correlate the exogenous hypoxia marker pimonidazole with the endogenous hypoxia-related marker carbonic anhydrase 9 (CA9) and with vascular and proliferation parameters.

**Methods:** Pimonidazole and the S-phase marker iododeoxyuridine (IdUrd) were administered intravenously to 43 patients with stage III-IV head and neck cancers before biopsies were taken. Microscopic slides were cut and stained by immunofluorescence for vessels, IdUrd, pimonidazole and CA9. Twenty-three patients were treated with radiotherapy plus hypoxic modification while the other patients received standard treatment.

**Results:** The distribution patterns of pimonidazole and CA9 were similar although CA9 was observed at shorter distances from blood vessels. Locoregional tumor control was significantly lower for patients who had hypoxic tumors or tumors with low vascular density. The 2-year control rates were 48% versus 87% for tumors with high and low pimonidazole binding levels ( $p=0.01$ ) and 48% and 88% for tumors with low and high vascular density ( $p=0.01$ ). These associations disappeared in the subgroup of patients treated with hypoxic modification. There was no relationship between the level of CA9 expression and treatment outcome. Proliferating cells were rarely observed in pimonidazole positive areas but were more frequent in CA9 positive areas.

**Conclusions:** Pimonidazole binding and vascular density can predict treatment outcome in head and neck cancer and may be useful as selection tools for hypoxia modifying treatments.

### **Whole body computed tomography in patients with newly diagnosed head and neck squamous cell carcinoma**

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**Background:** The presence of distant metastasis or an additional malignancy almost always results in a major alteration in the treatment of the patients with head and neck squamous cell carcinoma (HNSCC). The benefit of chest/abdominal computed tomography (CT) remains unclear. The aim of this study was to examine the impact of routine screening of whole body CT in the treatment of patients with newly diagnosed HNSCC.

**Methods:** The following patients were included: those with newly diagnosed T2-T4 head and neck squamous cell carcinoma (T3-T4 for glottic and lip cancers) and/or those with a cervical metastasis of squamous cell carcinoma. Only patients in whom curative treatment was estimated to be possible were included. The patients underwent CT scans of the thorax and abdomen.

**Results:** By now, we have examined 80 patients. The whole body CT had a major impact on the treatment of three patients. Two patients with large primary tumors had distant metastases. One patient had a large aortic aneurysm, which had to be treated before the cancer treatment. Additionally, there was a patient with aortic aneurysm, which was treated after the cancer treatment. Sixteen other patients had findings that needed further examination or follow-up. Ten of these patients had one or more further examinations done, in which nothing remarkable was found out.

**Conclusions:** Our results show that whole body CT had a major impact on the treatment in three out of the 80 patients (3.8%), but it caused unnecessary further examinations in several cases. Routine screening of whole body by CT does not seem warranted in patients with HNSCC, but it may be indicated for a more selected patient groups, such as those with abnormal chest x-ray, clinical suspicion of distant metastasis or patients undergoing a major microvascular surgery.

### **Incidence and prognostic relevance of tumor- and necrosis volume in carcinoma of the head & neck (by computed tomography scans)**

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**Background:** CT scans of patients with the equal tumor volumes of the carcinoma of the head and neck show differences in the contrast-material-accumulation. We investigated the impairment of tumor (TV)- and necrosis volume (NV) as prognostic factors. Possibly the hypoxic tumor volume could be a better prognostic factor than the total tumor volume.

**Methods:** From September of 1998 until December of 2001 in our department 60 patients (56 male, 4 female; mean age: 59 year, range 41-75 year) with primary inoperable squamous cell carcinoma of the head and neck were treated with an accelerated-hyperfractionated radiotherapy ad 70,6/72,8 Gy/77,6 Gy alone or in combination with a chemotherapy with mitomycin C or cisplatin and paclitaxel. In the pretherapeutic computed tomography scans the tumor volume of the primary (TV) and lymph nodes more than 1 cm in diameter were measured. The volume of all sites were calculated with the ellipsoid formula (volume =  $1/6 \times \pi \times a \times b \times c$  in  $\text{cm}^3$  with a, b, c being the largest diameters in the three dimensions). The total tumor volume (TV = area with contrast material accumulation) and the intratumoral necrosis volume (NV = intratumoral area without contrast material) were calculated in the same way.

**Results:** 59/60 patients were treated more than 70 Gy (mean: 71.4 Gy; range: 66-77.6 Gy). The mean treatment time was 40 days, range 31-57 days. From 60 patients 21 died, 19 because of the tumor progress or metastasis and two patients died because of other diseases. 39 are alive at the moment. The overall survival in all patients were 12 month. In 43/60 (72%) patients tumor necroses were present in CT-scans. In patients with necrosis area in the tumor the overall relapse-free survival was significant lower than in patients without necrosis areas ( $p=0,0014$ ). Tumor necroses was found to be an independent prognostic factor in multivariate analysis. Tumor volume and necrosis volume have had not influence of overall or event free survival.

**Conclusions:** In patients with necrosis area in the tumor in head and neck carcinomas the overall relapse-free survival is significant lower than in patients without necrosis areas.

**Keywords:** tumor volume, necrosis volume

### **The prognostic value of pretreatment lymph node parameters in the development of distant metastases in Head and Neck carcinoma:**

#### **Value of MRI-determined parameters**

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**Background:** To evaluate the prognostic significance of pretreatment MRI-related lymph nodes parameters with regard to the distant metastasis free interval (DMFI) in patients with head and neck squamous cell carcinomas (HNSCC).

**Methods:** Pretreatment MRI studies of 311 patients with HNSCC were reviewed for the presence of minimal-sized lymph nodes at specific levels as well as the presence of lymph node characteristics including extranodal spread, central necrosis and number and volume of ipsi- and contralateral lymph nodes. Of these patients, 174 (56%) had lymph nodes with an appropriate minimal size (axial diameter > 8 mm with exception at paratracheal and (retro) pharyngeal levels wherein the minimal diameter was 4 mm considered as minimal-sized).

**Results:** The 5-years DMFI among patients without minimal-sized on MRI was 85% compared to 72% among those minimal-sized lymph nodes on MRI. Among the study group with MRI minimal-sized lymph nodes, the presence of extranodal spread (ENS) as detected on MRI was the only independent prognostic factor associated with the DMFI ( $p = 0.002$ ). Based on this analysis, three risk groups regarding the DMFI could be identified. The low risk group (5-years DMFI: 86%) consisted of patients without minimal-sized

nodes on MRI. The intermediate risk group (5-years DMFI: 79%) consisted of patients with minimal-sized nodes on MRI without ENS. Finally, the high risk group (5-years DMFI: 55%) consisted of patients with minimal-sized nodes and ENS on MRI ( $p < 0.0001$ ).

**Conclusions:** MR imaging enables selection of patients with a high risk for developing distant metastases (DM). Patients with ENS assessed by MRI are at high risk for developing DM and should be qualify for screening for DM.

### **Ultrasound of the abdomen and total bone scintigraphy in patients with cancer of the head and neck**

S. Lybak, J. Olofsson (Bergen, Norway)

**Background:** All patients with head and neck cancer are examined by physical and radiological examinations of the primary cancer, neck and lungs. Most centres today also add bronchoscopy and oesophagoscopy to these examinations. In the present study we added ultrasound of the abdomen (112 patients) and total bone scintigraphy (118 patients). We wanted to find out the potential benefits of these additional examinations.

**Methods:** 118 consecutive patients admitted to our department with cancer within the head and neck region underwent additional examinations with ultrasound of the abdomen and total bone skeleton scintigraphy. Approximately 80% of the patients had a squamous cell carcinoma. All examinations were carried out on a routine basis. Bone scintigraphy was done as a whole body scan with  $99\text{m Tc} - 555 \text{ M Bq}$ . All patients have been followed up at our clinic after treatment.

**Results:** Bone scintigraphy showed 33 pathological results; 16 in columna, 9 in costae, 5 in primary site, 2 in kidney, 1 in humerus and 1 had a metastasis. All patients with pathological bone uptake were further evaluated with CT, but only one patient was diagnosed as having metastases.

Ultrasound of the abdomen showed pathological findings in 43 patients; cysts in the kidney (9), cysts in the liver (9), cholelithiasis (8), aneurysms of the aorta (6), haemangiomas in the liver (4), hydronephrosis (3), cysts in the pancreas (2), adrenal gland pathology (1), ascites (1) and liver metastases (1). The metastases in the liver were found in a patient with a low differentiated cancer of the ethmoidal region and were not known before. Blood samples taken a week after the ultrasound did, however, show elevated liver enzyme levels. No second primary cancers were found by the use of ultrasound.

**Conclusions:** By adding ultrasound of the abdomen and bone scintigraphy in the pretreatment evaluation of our head and neck carcinoma patients we only found two patients with distant metastases that would not have been detected without the two additional investigations. In addition we found one case of an aorta aneurysm that needed urgent treatment. The routine use of ultrasound of the abdomen and bone scintigraphy in our head and neck carcinoma patients have been stopped, even if the results greatly changed the treatment in 3 patients, but caused a lot additional investigations for unrelated reasons. Therefore ultrasound to the abdomen and bone scintigraphy will only be carried out on those patients where we find specific indications for such investigations.

### **Screening for distant metastases and synchronous primary tumours below the clavicles in patients with head and neck cancer: whole body FDG-PET or chest CT?**

R. de Bree, A. Senft, J. Brouwer, EFI. Comans, OS. Hoekstra, CR. Leemans (Amsterdam, The Netherlands)

**Background:** The detection of distant metastases at initial evaluation may alter the selection of therapy in patients with head and neck squamous cell carcinoma (HNSCC). In a recent study we retrospectively analysed the results of conventional screening for distant metastases in HNSCC patients and found that chest CT was the single most important diagnostic technique. FDG-PET is effective

tive in staging other tumours like lung carcinoma. The aim of this study was the comparison between chest CT and whole body FDG-PET in screening for distant metastases and synchronous primary tumours below the clavicles in patients with head and neck cancer

**Methods:** We prospectively studied the results of whole body FDG-PET and chest CT in 78 consecutive HNSCC patients at high risk for distant metastases.

**Results:** Distant metastases or synchronous primary tumours were found in 13 patients: PET and chest CT detected lung metastases in 6 patients and a primary lung carcinoma in 2 patients. FDG-PET detected also a primary hepatocellular carcinoma, an intra-abdominal adenocarcinoma and cervical spine metastases in one patient each, which were not detected by chest CT. Chest CT detected in 2 patients lung metastases, which were not detected by FDG-PET. FDG-PET was positive at other sites in 7 patients, which were not confirmed by conventional diagnostic techniques. CT-thorax was positive in another 7 patients, which was not confirmed during follow-up of at least 6 months.

**Conclusions:** FDG-PET can detect distant metastases and synchronous primary tumours in HNSCC patients and may be superior to current diagnostic work-up. Cost-effectiveness is under investigation.

#### Re-assessment of tumor volume during radiotherapy with anatomic and functional imaging: impact on target volume extension and on dose distribution.

V. Gregoire, X. Geets, JF. Daisne, T. Duprez, M. Hamoir, M. Lonneux (Brussels, Belgium)

**Background:** In three-Dimension Conformal Radiotherapy (3D-CRT) or in Intensity Modulated Radiotherapy (IMRT) of head and neck tumors, the Gross Target Volumes (GTV) are typically delineated on a contrast enhanced CT-scan performed before the start of treatment. Our group has already showed the potential usefulness of a pre-treatment FDG-PET, and the little added value of a pre-treatment MRI for the GTV delineation of pharyngo-laryngeal tumors. It is however anticipated that the tumor volume will progressively change during radiotherapy both from an anatomical and a functional point of view, addressing thus the usefulness of a re-imaging procedure during treatment. The aim of this study was to evaluate the usefulness of a re-assessment of the tumor volume during radiotherapy for pharyngo-laryngeal cancers, and to evaluate the impact of such procedure on the dose distribution on non-target tissues.

**Methods:** Twenty patients with squamous cell carcinoma of the oropharynx (n=10), hypopharynx (n=6) and the larynx (n=4) were prospectively enrolled. All patients were treated with curative intent by radiotherapy eventually combined with concomitant chemotherapy. After a dose of 46 Gy (range 40 to 48 Gy), all patients got a contrast enhanced CT-scan, an MRI (T1 without and with contrast enhancement, T2) and an FDG-PET. Image acquisition was performed using the immobilization mask. After image co-registration, the GTVs were delineated blindly. From these volumes, the Clinical Target Volumes (CTV) including the microscopic tumor infiltration, and the Planning Target Volumes (PTV) including the uncertainty in patient positioning were delineated using consistent guidelines. Dose distribution was then generated using 3D-CRT or IMRT on the various PTVs. All the volumes and the dose distribution were compared with their counterparts obtained from the pre-treatment images acquired in similar conditions.

**Results:** Compared to the pre-treatment figures, a significant reduction in the GTVs delineated from the per-treatment CT or MRI was observed. For oropharyngeal tumors, the average GTV dropped from 28.7 ml to 18.2 ml (p= 0.001), and from 27.8 ml to 12.6 ml (p=0.002), for CT and MRI, respectively. For hypopharyngeal and laryngeal tumors, the average GTV dropped from 20.7 ml to 14.2 ml (p= 0.037), and from 19.3 ml to 9.2 ml (p= 0.01), for CT and MRI, respectively. Data analysis for FDG-PET is in progress. Such difference in GTVs translated into significant reduction of both the CTVs and the PTVs. Using similar planning technique, the reductions in target volumes translated into a significant reduc-

tion in the irradiated volumes. For laryngeal tumors, in comparison with the plans performed from pre-treatment CT, the volume of the 95% isodose dropped from 93 ml to 60 ml and to 51 ml for plans generated from per-treatment CT and MRI, respectively. Corresponding volumes of the 50% isodose reached 226 ml for pre-treatment CT and 180 ml and 138 ml for the per-treatment CT and MRI, respectively. Analysis of the dose distribution for the pharyngeal tumors is in progress.

**Conclusions:** This preliminary study indicates that a significant reduction in the target volumes can be demonstrated using a second round of imaging modalities during radiotherapy. Such differences translated into significant differences in the irradiated volumes, which could open avenues for radiation dose-escalation and/or reduction in treatment morbidity.

#### Therapy evaluation of laryngeal carcinomas by tyrosine-PET

B. van der Laan, J. Boer, J. Pruijm, F. Burlage, A. Krikke, A. Tiebosch, F. Albers, W. Vaalburg (Groningen, The Netherlands)

**Background:** One of the major problems in head and neck oncology is determination of tumor status after radiotherapy. Positron Emission Tomography (PET) can determine tumor metabolism in vivo. The feasibility of TYR-PET with L-[1-<sup>11</sup>C]-Tyrosine (TYR) as a tracer for therapy evaluation of laryngeal squamous cell carcinomas after radiotherapy was investigated.

**Methods:** Nineteen patients with laryngeal carcinomas underwent a TYR-PET scan (PET1) before definitive treatment. The second TYR-PET scan (PET2) was performed 3 months after radiotherapy. During the minimal follow-up period of 24 months, 6 patients had clinical suspicion of recurrent disease. In these six patients a third TYR-PET (PET3), CT imaging and biopsies were performed.

**Results:** All pretreatment tumors were depicted by TYR-PET (PET1). Three months after radiotherapy, sensitivity and specificity of TYR-PET (PET2) for discrimination between residual tumor and post treatment tissue changes, were both 100%, and for CT, 50% and 67%, respectively. For detection of recurrent tumor during follow-up, sensitivity and specificity of TYR PET (PET3) were also 100%, and CT, 75% and 50%, respectively. TYR-PET proved favourable compared to histological confirmation of residual or recurrent tumor by biopsy.

**Conclusions:** Dynamic TYR-PET is an accurate imaging modality for therapy evaluation in detection of residual as well as recurrent disease.

#### FDG-PET scan in local follow-up of irradiated head and neck squamous cell carcinomas

S. Herve, C. Conessa, E. Roguet, S. Talfer, P. De Rotalier, JL. Poncet (Paris, France)

**Background:** The aim of this prospective study is to assess the value of Positron Emission Tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) in prediction of local control in irradiated Head and Neck Squamous Cell Carcinomas (HNSCC).

**Methods:** 42 patients with irradiated HNSCC underwent 49 FDG-PET between 3 and 6 months after the end of radiotherapy. The mean follow-up time after first FDG-PET was 17 months.

**Results:** FDG-PET was a true positive in 6 patients, a false positive in 7 patients and a true negative in 29 patients. Sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were of 100%, 80%, 46% and 100% respectively.

**Conclusions:** FDG-PET is useful for prediction of therapy outcome in irradiated HNSCC. No biopsy is needed for at least one year if FDG-PET is negative. If it is positive and the biopsy is negative, a decreased FDG uptake measured in a follow-up scan indicates that a local recurrence is unlikely.

### Fused PET/CT imaging for post-treatment monitoring in advanced head and neck cancer

H. Witherow, N. Kalavrezos, B. Swinson, M. Saunders, L. Newman (London, United Kingdom)

**Background:** Posttreatment monitoring of advanced head and neck malignancy is of paramount importance. However the distorted anatomy and scar tissue formation following surgery and radiotherapy may challenge conventional imaging methods. Conventional 18F-2-fluorodeoxyglucose (FDG) positron emission tomography (PET) is sensitive for disease recurrence but accurate localisation of FDG abnormalities in the head and neck is difficult. The recent introduction of PET/CT which provides fused PET and computed tomographic images should overcome this problem. The aim of this prospective clinical trial carried out in an University Teaching Hospital is to detect and accurately locate recurrent disease or second primary lesions in head and neck cancer patients treated for advanced head and neck cancer with surgery and radiotherapy.

**Methods:** 24 consecutive head and neck cancer patients treated with surgery and radiotherapy were submitted to clinical examination, Magnetic Resonance Imaging (MRI), and fused PET/CT imaging. Suspicious lesions were biopsied and imaging results were compared with the definitive histology.

**Results:** Disease was confirmed following biopsy in 9 of the 24 patients. Clinical examination and MRI failed to detect recurrence in 5 patients whereas PET/CT detected all but one. Specificity of MRI was 60% and sensitivity 40%. PET/CT was 90% specific and 80% sensitive.

**Conclusions:** Fused PET/CT imaging has the highest sensitivity and specificity rate in the post-treatment monitoring group of head and neck cancer patients. Detection of abnormal metabolic activity with anatomical co-localisation as provided by PET/CT imaging may help the early identification of recurrent disease or second primary lesions allowing the timely institution of potential salvage treatment.

### Reconstruction of fronto-orbital defects after tumor and trauma surgery

K. Aitasalo, R. Grenman (Turku, Finland)

**Background:** Subcranial craniotomy consists of the concept to enable exposure to the skull base from the anterior direction under direct vision avoiding frontal lobe retraction.

**Methods:** A retrospective review was conducted of the results of 68 patients (43 men and 25 women), who underwent this procedure from 1996 to 2002 in our ENT Department. The mean age of the patients was 45 years. Tumors and traumas involved the nasopharynx, the paranasal sinuses, the orbit or the meninges. 12 of these patients were preoperatively irradiated to a dose of 60-65 Gy.

**Results:** In all cases the tumor resections and reconstructions were tolerated with good functional and cosmetic results. In dura constructions we have used fascia lata with fibrin glue to seal the entire defect in the skull base. In the extensive reconstructions of the skull base we used bone substitutes such as bioactive glass or hydroxyapatite. The bone transplants were fixed with titanium or resorbable plates and screws. All 23 benign and 16 of the 22 patients (72%) with malignant nasopharyngeal tumors are alive with a follow-up of 30 mo. In addition we have closed a large cerebrospinal fluid leak in 11 cases and an optic nerve decompression was performed after frontobasal traumas in 12 cases. Significant complications consisted of onemeningitis occurring in one patient and one partial flap necrosis in the frontal area. The common late complication was total or partial olfactory dysfunction (62%).

**Conclusions:** The reconstruction with the bioactive materials such as bioactive glass and/or hydroxyapatite is associated with a low morbidity and a good functional result in skull base surgery with reduced hospitalization time. This subcranial craniotomy with new reconstruction materials is a safe, versatile and effective procedure.

### Three-dimensional multitissular reconstruction of midfacial defects: A rationale for the use of flaps in complex challenging problems

B. Lengele, D. Meunier, A. Lona, Ph. Rombaux, M. Hamoir (Brussels, Belgium)

**Background:** In order to rationalize the use of flaps for the reconstruction of complex multitissular defects created after the oncological resection of midfacial tumors, we defined anatomical guidelines for the selection of tissue transfers according to the location, size and the nature of the craniofacial defect.

**Methods:** Five anatomical units are considered in the preoperative assessment of the tumor, then in the peroperative evaluation of the surgical defect: They include the orbit (I), the nasal lining (II), the hard palate (III), the skull base (IV) and the hard and soft tissue contour of the face (V). The common reconstructive concept underlying the guidelines is that the flap has to include in adequate spatial relationships, one distinct tissular component for each missing unit of the facial framework.

**Results:** 25 patients with invasive midfacial tumors of various origins were operated according to these principles. 23 were reconstructed with free flaps, only 2 cases being treated with local flaps from the temporal fossa. In 10 cases, plicated rectus abdominis free flaps were used to reconstruct mid-sized defects involving the units I, II and partially the posterior hard palate (IIIb). In larger defects including also the whole premaxilla (IIIa), the skull base (IV) and large areas of the facial skin (V), combined "chimaeric" flaps of the subscapular system were selected (9 cases). Smaller free flaps (1 gracilis, 2 preauricular) were also used to improve secondary the cosmetic and functional results in 3 patients.

**Conclusions:** This algorithm allowed us to achieve excellent oral and nasal functional results in all patients with an adequate oncological control and an acceptable facial appearance.

### Use of titanium Vascular Staple (VCS) system for venous microvascular anastomosis in free-flap surgery for orofacial reconstruction Closure

R. Morrison, J. McMahan (Glasgow and Sheffield, United Kingdom)

**Background:** Use of titanium Vascular Closure Staple (VCS) clips as an alternative to sutures is becoming more widespread in microvascular surgery. Their use has been shown to be at least as effective as suturing, with a significant reduction in time taken for each anastomosis in many studies. This study describes our experience of VCS clips for venous anastomosis in 35 free-flaps used in orofacial reconstruction. 11 of the later anastomoses were also timed.

**Methods:** 38 venous anastomoses were carried out on 35 free-flaps between May 2000 and April 2003. The technique used in each case involved placement of four 9/0 ethylon stay sutures at 90deg to each other. The anastomosis was then completed using titanium VCS clips (manufactured by Autosuture). For anastomoses performed after July 2002 (11 cases) the procedure was timed from placement of the first stay suture until the last VCS clip. In cases performed before July 2002 information was gathered retrospectively from casenotes. Data collection included type of flap used, number of venous anastomoses in each pedicle, any re-exploration of anastomoses, any flap failure and in 11 cases, time to complete anastomosis.

**Results:** Of the 35 free-flaps performed only one required re-exploration of the pedicle and subsequently failed. This failure was not attributed to venous circulatory failure. The 11 timed anastomoses showed that the mean time for completion was 12mins 32secs (range 9mins 30secs to 15mins).

**Conclusions:** Our clinical experience along with that of other studies supports laboratory evidence that microvascular anastomosis with VCS clips is at least as efficacious as sutured anastomoses. VCS may clips have the added benefit of reducing operating time.

### Major glossectomy for locally advanced but resectable carcinoma of tongue: analysis of 94 cases

H. Devalia, PS Pai, AK D'Cruz  
(Carlshalton, United Kingdom and Mumbai, India)

**Background:** Major glossectomy is considered to be one of the most mutilating procedures in surgery. The aim of this study was to evaluate oncological safety and functional outcome after radical glossectomy for advanced but resectable carcinoma of tongue.

**Methods:** This is a retrospective review of 94 patients who underwent radical glossectomy in 7 years period. They had total or sub-total glossectomy with appropriate radical neck dissection and reconstruction of floor of mouth. Larynx was preserved in all except 2 patients. 70 patients had temporary tracheostomy. 39 patients could complete postoperative radiotherapy. At the time of presentation there were 08 patients with T2 primary tumour, 09 with T3 and 77 with T4. There were 40 patients with N0 neck disease, 22 with N1, 31 with N2 (N2a N2b, N2c) and 1 with N3 neck disease. Major glossectomy was done as salvage procedure following recurrence in remaining 29 patients. Reconstruction of the defect was accomplished using pectoralis major myocutaneous flap (PMMC) in 81 patients.

**Results:** There was no perioperative mortality. 31 patients had partial flap necrosis and 16 had orocutaneous fistulas. Resumption of swallowing was achieved in 72 patients in 6 weeks. 42 patients had recurrence within 10 months. Among the recurrences, there were 15 local (15.96%), 14 regional (14.89%), 10 locoregional (10.64%), 2 with local recurrence (2.13%) and distant metastases while one patient had distant metastasis (1.06%). Two and five year survivals were 55.32% and 44.68 % respectively. Lymph node involvement was a poor prognostic factor and it was statistically significant while perineural infiltration was not statistically significant.

**Conclusions:** In advanced but resectable carcinoma of tongue, radical glossectomy provides local and regional control and it can result in an acceptable and meaningful survival in properly selected patients.

### A clinical approach to oral function assessment in rehabilitation of patients after oral cancer

R. Thompson, M. Jackson, F. Dawson, T. Jackson, A. Brown, AG. Robertson, IG. Camilleri, DS. Soutar  
(Glasgow, United Kingdom)

**Background:** Combined treatment of SCC's of the oral cavity can result in physical impairment and emotional disruption, diminishing patients' Quality of Life. Measures of functional impairment are useful in monitoring patients' progress throughout their rehabilitation. However "hi-tech tools", such as transit times on video-fluoroscopic swallow studies, have a poor correlation with patients' symptoms. The aim of this study was to develop a set of measurements of oral function, based on our patients' most symptomatic impairments after combined treatment. (The simplicity of this assessment will be shown in a powerpoint video clip.)

**Methods:** Prospective study of 70 patients, in whom oral carcinomas were excised and reconstructed. Many also required post-operative radiotherapy and/or chemotherapy. All were treated at Canniesburn between 1999 and 2002, with a minimum 6 months follow-up. Design and Outcome Measures: Patients are examined clinically, assessing the functional integrity of the cranial nerves. Mandibular and tongue movements were measured. Patients' recovery of function was scored according to the University of Washington Quality of Life, EORTC QLQ, Therapy Outcome Measures and Functional Intraoral Glasgow Scale.

**Results:** There was an impressive correlation between the physical impairments revealed by this assessment and the oral function symptoms reported in the Quality of Life questionnaires. Alcohol abuse, anxiety and depression played a major role in incomplete rehabilitation

**Conclusions:** The restoration of good oral function, minimises the deterioration in Quality of Life after treatment for oral SCC. This

clinical assessment is quick, inexpensive and acceptable to patients. It allows us to standardise a critique of our reconstructions to optimise them.

### Reconstruction of the upper jaw using microsurgical free flaps: classification of the defects and surgical options.

R. Cocchi, D. Fasano, FM. Montanari, MG. Pennesi, S. Stea, L. Lancellotti (Bologna, Italy)

**Background:** The classification of Cordeiro is probably the most appropriate for reconstructive purposes after resection of the upper jaw. We feel that an additional subdivision is useful in improving the choice of reconstructive options. We use the following: A) limited maxillectomy: resection of a wall of the upper jaw; B) lower sub-total maxillectomy: resection of the lower 5 walls of the upper jaw conserving the orbital floor; C) upper subtotal maxillectomy: resection of the 5 upper walls conserving the palate; D) total maxillectomy + resection of 6 walls of the jaw; E) total maxillectomy + exenteratio orbitae; F) orbitomaxillectomy: exenteratio orbitae + resection of the 5 upper walls of the jaw conserving the palate.

**Methods:** During the last five years we've considered 21 neoplastic patients. In Group A, 4 free flaps of the forearm and one of the fibula were carried out; in Group B, 3 rectus abdominis flaps, 1 of the fibula and 1 of the osteocutaneous scapular; in Group C, 2 osteocutaneous scapular flaps; in Group D, 4 rectus abdominis flaps; in Group E, 2 rectus abdominis flaps and one of the latissimus dorsi; in Group F, 1 rectus abdominis flap and 1 osteocutaneous flap of the latissimus dorsi.

**Results:** In no instance was there necrosis; in 2 cases, a revision of the anastomosis was carried out. Three patients died in the first 6 months after surgery, with a survival rate of 65% and a follow-up which varies from 1 month to 5 years.

**Conclusions:** In our experience, an expansion of Cordeiro's classification allows us to program surgery more accurately, choosing the most appropriate option for each group of bone resection.

### Micro-vascular tissue transfer for mandibular reconstruction in carcinology

JP. Rame, MY. Louis, D. de Raucourt, A. Bouvet (Caen, France)

**Methods:** From October 1995 to April 2003, 56 bone or composite flaps were carried out, either simultaneously with mandibular resection (complementary radiotherapy can therefore take place after the 6<sup>th</sup> week) or later, often due to complications resulting from other treatment modalities (osteoradionecrosis). Many of these acts were therefore carried out on an irradiated site without increasing the level of complications.

**Results:** The free fibula flap was the first used. Flap elevation is relatively simple and can be realised at the same time as tumour resection. A long bone length is available (25cm) and several osteotomies are possible. The fibula skin paddle which can rotate via the bone enables restoration of the floor of the mouth. After consolidation, and even after radiotherapy osteo-integrated dental implants can be considered. We carried out 18 free fibula flaps with one failure. No sequelae were noted on the donor sites.

In our Centre the scapular flap is the most frequently used. Flap elevation necessitates a double position change during surgery. 10cm bone length is available and one osteotomy is possible. On the same pedicle, using the same access, different independent soft tissue flaps can be elevated (latissimus dorsi, serratus, skin) allowing complex reconstructions: mandible, mouth floor, tongue, cheek... The correct diameter of the pedicle allows reliable use of this technique. We performed 38 scapular flaps without total or partial failure and without shoulder sequelae providing that physiotherapy is delivered.

**Conclusions:** Pelvi-mandibular reconstruction remains a significant surgical act whose cosmetic result is often satisfactory; the functional result depends on soft tissue defects. This technique is particularly indicated in anterior or antero-lateral bone defects, and in patients with correct general condition Competence in several

techniques enables adapting the reconstruction to local and general status.

### **Functional reconstruction of the supraglottic region with a free radial forearm flap and septal cartilage to rehabilitate swallowing**

M. Bloching (Halle, Germany)

**Background:** Patients with supraglottic laryngectomy often complain about persisting dysphagia, because the resection involves the most important protective mechanisms of the airway. The additional resection of parts of the tongue base or the lateral hypopharyngeal wall leads to increasing aspiration problems. The aim of our study was to establish a functional reconstruction of the supraglottic region after an extended resections of the base of tongue and the lateral pharyngeal wall. To reach this goal, we used a free radial forearm flap in combination with septal cartilage to stabilize the reconstructed epiglottis.

**Methods:** The reconstruction of the supraglottic region with a free radial forearm flap and septal cartilage in extended oro-hypopharyngeal and laryngeal carcinomas was carried out in 7 patients in the time from 1997 - 2002. The postoperative results were evaluated taking into consideration the closure of the perioperative tracheostomy, the perioperative degree of aspiration and the quality of speech. In one patient the reconstruction was performed in a second stage procedure after extended endoscopic laser resection.

**Results:** Closure of tracheostomy in 4 of 7 patients within the first year postoperative. All patients are able to speak in a sufficient manner and in 5 of 7 patients oral alimentation is possible.

**Conclusions:** The preliminary results show that a functional reconstruction of the supraglottic region with a free radial forearm flap and septal cartilage to reconstruct the epiglottis helps to avoid chronic aspiration and to preserve the larynx.

**Key-words:** Extended supraglottic laryngectomy, free radial forearm flap, neoepiglotis

### **Micro-vascular tissue transfer for repair of head and neck cancer defects: 8 years experience**

JP. Rame, MY. Louis, D. de Raucourt, H. Soufarapis (Caen, France)

**Methods:** From March 1995 to April 2003, 141 free flap reconstructions were carried out in the head and neck cancer surgery department: 47 jejunum, 16 latissimus dorsi, 20 forearm f, 2 free omentum, 18 fibula, and 38 scapular flaps. They were performed either simultaneously with tumoral resection, or during rehabilitation of sequelae or complications (pharyngostenosis, radionecrosis...). 50% of these acts were therefore performed in an irradiated site and we will analyse these results and indications. 14 flaps failed: 9.9%.

**Results:** The jejunum flap is used for circular pharynx reconstruction (simple tube, partly open tube, large U-shaped tube) It is an inevitable flap but, in our experience, the most fragile: 8 failed out of 47. The latissimus dorsi flap applies to two indications: large defects in the cephalic area and the restoration of total glossectomies without laryngectomy, the second being currently reviewed due to carcinological prognosis (16 latissimus dorsi flaps carried out, 2 necroses). Widespread defects of small depth are repaired using forearm flaps (pharynx wall, floor of the mouth, palate, cheeks...). Two flaps out of 20, failed. The free fibula flap (bone or composite) was our first technique used for mandible reconstruction. It is necessary for long bone defects requiring several osteotomies. (18 carried out, 1 failed). The free scapular flap offers bone and other independent soft tissue. It is currently the most frequently adopted and the most reliable (38 carried out, no failure).

**Conclusions:** Free flap reconstruction is a technique perfectly adapted to carcinological head and neck surgery. The duration of surgery and level of necrosis should be taken into account when defining indications. Ideally, competence in several techniques for each indication enables to adapt reconstruction to the local and general conditions of each patient.

### **Microvascular free tissue transfer for restoration of head and neck defects: a clinical review of 20 years**

A. Eckardt, JE. Hausamen (Hannover, Germany)

**Background:** Tissue defects in the head and neck region have long been a challenge for reconstructive surgery. Substantial patient morbidity and high surgical complication rates were common consequences of pedicled, staged flaps. During the last three decades, tremendous progress has been made in the field of reconstructive surgery, in particular due to the introduction of free vascularized tissue transfer. For defect restoration of the oral cavity/oropharynx various sites are available today.

**Methods:** Between March 1982 and December 2002 a total of 570 free flap reconstructions were performed among 529 patients. Among the 550 reconstructions 480 patients suffered from head and neck tumors of various pathologies. In 49 patients free flap reconstructions were performed for other conditions like trauma, osteoradionecrosis, congenital defects.

**Results:** Regarding the donor site selection the free jejunum predominated with 181 reconstructions (32.9%), followed by the radial forearm flap in 170 reconstructions (30.9%). 80% of the reconstructions were immediately performed following resection of the tumor. Our complication rate is comparable with those complications reported in the literature ranging from 2% to 12%. In our patient population surgical reexploration was necessary in 39 patients (7.3%); the total failure rate with flap necrosis was 6%. The overall success rate was 94%. At our institution the radial forearm flap, the latissimus dorsi flap, and the fibula have become the workhorse donor sites for most defects. Significant risk factors for developing local graft related complications were age >60 years (p=0.021) and surgery time > 8 hours (p=0.043).

**Conclusions:** In advanced head and neck tumors microvascular free tissue transfer can be regarded as a "gold standard" today and is a safe and reliable procedure in carefully selected patients.

### **A UK multi-centre pilot study of speech and swallowing outcomes following head and neck cancer**

K. Radford, H. Woods, D. Lowe, S. Rogers (Liverpool, United Kingdom)

**Background:** Speech and swallowing are important components of health-related quality of life (HRQOL) following head and neck cancer treatment. The aim of this study was to demonstrate the value of prospective multi-centre evaluation by Speech and Language Therapists (SLT) and compare HRQOL with speech and swallowing impairments.

**Methods:** The University of Washington Head and Neck questionnaire version 4 (UW-QOL) and Therapy Outcome Measures (TOM) were rated before and six months after cancer treatment in ninety-five patients from twelve centres.

**Results:** There was deterioration in TOM scores at six months. Pre-treatment UW-QOL swallowing was ranked equal first, with speech fourth. At six months speech was first and swallowing second. There were positive correlations between UW-QOL swallowing and TOM dysphagia and between UW-QOL speech and TOM laryngectomy, voice, phonology and dysarthria disorders.

**Conclusions:** Both outcome measures are suitable for routine practice. Adaptation of TOM scales for use with head and neck cancer patients may improve sensitivity, validity and therapist compliance. This study is the first of its type in the United Kingdom and as will be described forms a platform for further multi-centre head and neck outcomes research.

### **Different methods of 3D-conformal intensity modulated radiotherapy (IMRT) allow for parotid sparing in advanced head and neck carcinoma (HNC)**

T. Wendt, N. Abbasi, H. Salz, S. Liesenfeld (Jena, Germany)

**Background:** Radical radiotherapy often result in chronic xerostomy in long term survivors.

**Aims:** IMRT offers a non-homogenous dose distribution allowing for normal tissue sparing. Due to vicinity of tumor to be irradiated and organs like parotid gland or temporo-mandibular joint to be spared in the head and neck region even with IMRT sparing is difficult to achieve.

**Methods:** 11 patients were prospectively treated by IMRT with 3D-modulator technique (in-house development). According to supposed risk the prescribed dose was 64 to 70 Gy and 48-50 Gy in high and low risk volumes respectively. Recalculation for IMRT with step and shoot technology (Konrad®-System) was performed using the same treatment criteria. Clinical outcome was scored by quantitative scintigraphy and clinically.

**Results:** Median radiation dose at one parotid gland was restricted to 25.5 (21-46) Gy using 3D-modulator technique. With step and shoot IMRT similar doses were achieved. Total doses of 26 Gy or less seem to preserve parotid function. Step and shoot IMRT resulted in higher total body doses which might trigger secondary cancer in long term survivors.

**Conclusions:** Further analysis is warranted to define the optimal place of different techniques of IMRT at different clinical settings. Changing target volume definitions may facilitate normal organ sparing but needs extensive clinical testing.

#### **Endoscopic treatment of early glottic cancer and severe dysplasia/carcinoma-in-situ; the basis of laryngeal preservation.**

R. de Bree, AJGE. Peeters, KM. Goor, JA. Langendijk, M. van Agthoven, CR. Leemans, HF. Mahieu (Amsterdam, The Netherlands)

**Background:** For early glottic cancer are several treatment options available: radiotherapy, CO<sub>2</sub>-laser and (partial) laryngectomy. The aims of this study is to assess oncological, functional and cost-effective outcome of endoscopic treatment for severe dysplasia/carcinoma-in-situ and early (T1a) cancer of the glottis.

**Methods:** Prospective study of 216 patients who were endoscopically treated by means of endoscopic treatment (cordectomy type 1 and 2) for severe dysplasia/carcinoma-in-situ (n=107) or T1a glottic carcinoma (n=109) with a mean follow-up of more than 48 months. Thirty-nine patients underwent radiotherapy for T1a glottic carcinoma. Tumour status, voice quality and overall costs were determined.

**Results:** In the severe dysplasia/carcinoma-in-situ group 8 patients (7%) developed recurrence or conversion to squamous cell carcinoma, 6 of whom were successfully re-treated endoscopically. Two patients were irradiated, one of whom eventually underwent laryngectomy. In the T1a group 9 patients (8%) developed recurrence, two of whom were successfully re-treated endoscopically. Seven patients were irradiated. None underwent laryngectomy. Six patients developed a second or third laryngeal tumour which was treated with preservation of the larynx (CO<sub>2</sub>-laser or RT). Voice quality was better and the overall costs were lower for patients treated with CO<sub>2</sub>-laser as compared to radiotherapy.

**Conclusions:** Assuming that the cure-rate is identical for endoscopic treatment and radiotherapy and considering that post-radiotherapy recurrence usually leads to laryngectomy (occasionally partial), 23 of these patients (11%) probably would have undergone laryngectomy if they had been treated by radiotherapy initially. Thanks to endoscopic treatment only 1 patient (0.5%) lost his larynx. Because of ultimate laryngeal preservation, voice quality and cost-effectiveness endoscopic treatment is the treatment of choice in patients with early glottic carcinoma amenable for endoscopic treatment.

#### **Carbon dioxide laser microsurgery for Tis, T1 and selected cases of T2 glottic carcinoma**

R. Puxeddu, GP. Ledda (Cagliari, Italy)

**Background:** Among the different laryngeal neoplasms, glottic carcinoma is known to be one of the most suitable for functional

management. Nevertheless, the best treatment for Tis, T1 and T2 glottic carcinoma, whether an open neck procedure, endoscopy or radiotherapy, with reference to recurrence, survival, and functional results, has long been debated.

**Methods:** Retrospective study of 103 patients with well to undifferentiated glottic carcinoma (14 Tis, 68 pT1a, 14 pT1b, and 7 pT2 with impairment of vocal cord mobility) were treated from October 1993 to June 2001 at the Section of Otorhinolaryngology of the Department of Surgical Sciences and Organ Transplantations of Cagliari University. Mean follow-up was 3.9 years. Methods: Surgical treatment included endoscopic CO<sub>2</sub> laser cordectomies from type I to type Vc, according to the classification proposed by the European Laryngological Society in 2000.

**Results:** According to the Kaplan-Meier method, the probability of remaining free of local recurrence 3 years after primary surgery was 100% for the Tis group, 93.4% for the T1 group (S.E. 3.85%) and 100% for the T2 group. Local control at 3 years after exclusive CO<sub>2</sub> laser salvage surgery was 94.95% (S.E. 3.54%). The probability of remaining free of local recurrence 3 years after any type of salvage surgery was 100% for all the classes. Laryngeal preservation was achieved in 100% of the cases. Anterior commissure spread (AC1-AC2) resulted in a not statistically significant difference in local control (P=0.6), between the group of patients without (96.54%; S.E. 2.43%) and with anterior commissure involvement (87.5%; S.E. 11.69%).

**Conclusions:** In our experience, endoscopic laser excision offered an oncological valid alternative to the traditional open neck techniques and radiotherapy.

**Key words:** Larynx – Glottic carcinoma – Laser Treatment – Endoscopy

#### **Tumors of the laryngo-tracheal junction: the role of crico-tracheal resection and anastomosis**

C. Piazza, G. Peretti, A. Bolzoni, P. Nicolai, AR. Antonelli (Brescia, Italy)

**Background:** Crico-tracheal resection and anastomosis (CTRA) is mostly applied to benign subglottic stenoses. Aims: To describe our experience in approaching selected cases of laryngo-tracheal junction (LTJ) tumors by such an organ-sparing technique.

**Methods:** Between September '96 and April '02, we performed CTRA in 43 patients, 12 of whom (28%) were affected by LTJ tumors (age range, 18-74 years; mean, 46.5; male:female ratio, 7:5). Four of these were thyroid neoplasms involving the airway (3 papillary carcinomas, 1 metastasis from rectal adenocarcinoma), and 8 primary LTJ tumors (2 low-grade mucoepidermoid carcinomas, 1 pleomorphic adenoma, 1 adenoid cystic, 1 squamous cell carcinoma, and 3 low-grade chondrosarcomas).

**Results:** The extent of resection ranged between 2 and 5 tracheal rings, with excision of the cricoid arch in 6 cases, and of the arch plus part of the cricoid plate in 5. Complications occurred in 3 patients (cervical emphysema and pneumomediastinum, anastomotic partial dehiscence, and neck seroma with transient unilateral recurrent palsy). They were treated by temporary (6-18 days) tracheotomy in 2 cases and anastomosis revision in another. Endoscopic and radiologic follow-up did not reveal any local-regional recurrence (range, 4-79 months; mean, 28). Lung metastases developed in 3 patients with thyroid cancer.

**Conclusions:** CTRA can be considered a conservative option for selected LTJ tumors in which the endoscopic approach either failed or was thought unfeasible. Contraindications include distant metastases, previous high-dose RT on the neck and/or upper mediastinum, crico-arytenoid joint infiltration, anterior commissure and/or vocal cords involvement, massive thyroid cartilage invasion, bilateral recurrent palsy, pharyngo-esophageal full-thickness infiltration, and cranio-caudal extension greater than 5 cm.

### Continuous accelerated 7-days a week radiotherapy for head and neck cancer –

#### 5-year results of randomized clinical trial

K. Skladowski, B. Maciejewski, M. Golen, R. Tarnawski, K. Slosarek, R. Suwinski, M. Sygula, A. Wygoda (Gwilice, Poland)

**Background:** To evaluate clinical effectiveness of continuous accelerated irradiation (CAIR) alone for head and neck cancer treatment.

**Methods:** 100 patients with oral cavity, pharynx and larynx cancer in stage T<sub>2-4</sub>N<sub>0-1</sub>M<sub>0</sub> were randomized between two treatment arms: accelerated fractionation – 7-days a week (including weekends) and conventional – 5-days a week. Hence the overall treatment time was 2 weeks shorter in CAIR. Fraction dose of 2.0Gy and then 1.8Gy, delivered once a day to 66-72Gy, was the same in both arms.

**Results:** 5-year local tumor control was 73% in CAIR and 31% in control (p<0.0001). Tumor-cure benefit, especially pronounced for locally advanced lesions (T3-4), corresponded with significant improvement in 5-year disease-free and overall survival rates. Confluent mucositis (CM) was the main acute toxicity with incidence significantly higher in CAIR patients than in control ones (respectively - 94% vs. 53%). When 2.0Gy fractions were used radiation necrosis developed in 5 patients (22%) in the CAIR, as a typical consequential late effect (CLE). When fraction size was reduced to 1.8Gy no more CLE occurred, and 5-year RTOG grade III-IV late morbidity rate is similar in both arms (11% in CAIR and 9% in control).

**Conclusions:** This is a first randomized study on cancer radiation treatment where weekends were included into the working days, in order to accelerate the treatment and to avoid any inter-fraction gaps longer than 1 day. Although this report is based on the relatively small group of patients, its results have pushed us to use the accelerated 7-days fractionation of 1.8Gy per day in a standard radiation treatment for moderately advanced (T<sub>3-4</sub>N<sub>0-1</sub>) head and neck cancer patients. Furthermore, CAIR experience strongly suggests that at least for some head and neck cancers the routine practice of weekend radiation-gap could be disadvantageous.

### Aggressive simultaneous radiochemotherapy with cisplatin and paclitaxel in combination with accelerated-hyperfractionated radiotherapy in locally advanced head and neck tumors – results of a phase I-II trial

A. Sandner, Th. Kuhnt, J. Dunst, M. Bloching (Halle, Germany)

**Background:** Simultaneous radiochemotherapy (RCT) is the treatment of this choice in locally advanced head&neck cancers. We have tested a very aggressive combination protocol with cisplatin escalated paclitaxel in combination with accelerated-hyperfractionated radiotherapy to access the maximal tolerated dose (MTD), dose-limiting toxicity (DLT), overall toxicity and response rate.

**Methods:** The trial recruited 24 patients (21 male, 3 female, mean age 57 years) from 1998 through 2001 at our department. Radiation was administered with daily doses of 2Gy up to 30 Gy followed by twice daily 1.4Gy up to 70.6Gy to the primary tumor and involved nodes and 51Gy to the clinically negative regional nodes. The chemotherapy schedule included cisplatin in a fixed dose of 20 mg/m<sup>2</sup> on days 1-5 and 29-33 and paclitaxel at increasing dose levels of 20, 25, 30 mg/m<sup>2</sup> twice weekly over the whole treatment time. Patients were recruited in cohorts of 3 to 6 patients and the MTD was reached if 2 out of six patients in one cohort developed DLT. DLT was defined as any grade 4 toxicity or any grade 3 toxicity requiring treatment interruption or unplanned hospitalisation or any grade 3 neurotoxicity. We recruited mainly patients with large tumors for this protocol; all patients were stage IV and the mean tumor volume (primary + metastases) was 72±61cm<sup>3</sup>. The mean follow-up was 30 months (range 4-39 months).

**Results:** In summary, 6 patients have died of local tumor progression (N=2), distant metastasis (N=2) or therapy-related (N=2) dur-

ing follow-up. The 3-year overall survival was 71%. Tumor volume was not a risk factor for failure in this protocol (mean tumor volume in relapse-free versus progressive patients 74±60 cm<sup>3</sup> vs. 70±67 cm<sup>3</sup>). All patients have so far developed only slight late effects (fibrosis, lymphedema) with no grade 3-4 sequelae.

**Conclusions:** This very aggressive radiochemotherapy protocol yielded excellent response and survival figures but was associated with a very high rate of acute toxicity (8% therapy-related deaths). A maximal supportive treatment was required.

**Keywords:** radiochemotherapy, cisplatin, paclitaxel

### Response rate and outcome of a novel induction chemotherapy regimen (TPF) in the first line therapy of advanced head and neck carcinomas

R. Knecht, M. Baghi, M. Hambeck, H. Tesch, W. Gstöttner (Frankfurt, Germany)

**Background:** Induction chemotherapy of advanced head and neck cancer usually consists of two to three cycles of cisplatin 100mg/m<sup>2</sup> and 5-fluorouracil 5000mg/m<sup>2</sup>. More recently taxanes were added to this regimen especially in unresectable and recurrent disease. We have conducted an organ preservation study (phase II) from which we present for the first time the response rate of the triple regimen Taxotere, Cisplatin, 5-Fluorouracil (TPF) in the first line therapy of advanced resectable head and neck cancer.

**Methods:** 48 patients with resectable stage III/IV cancer of the oropharynx and hypopharynx were treated with three cycles of induction therapy with docetaxel 75mg/m<sup>2</sup> on day 1, cisplatin 100mg/m<sup>2</sup> on day 1 and 5-Fluorouracil 1000mg/m<sup>2</sup> on days 1-5 repeated every 3 weeks followed by concomitant radiotherapy. Radiation dosis was 70Gy (2Gy per day, 7weeks), chemotherapy was applied on days 1, 22, 43 of the radiation course. Response rate of the induction chemotherapy was confirmed by magnetic resonance imaging and surgical biopsies based on WHO guidelines.

**Results:** After induction chemotherapy we observed 31 complete responses, 10 partial responses and 7 progressive diseases, for an overall response rate of 85%. Carcinomas of the oropharynx had a slightly higher response rate (CR: 10/17, PR: 7/17) than carcinomas of the hypopharynx (CR: 21/31, PR: 3/31, PD: 7/31). Reversible neutropenia up to grade 4 was the most common toxicity. Regular follow up of the patients with a median observation period of 17 month revealed up to date one non tumour related death, 2 local-regional recurrences (hypopharynx) and 3 cases with metastatic disease in lung or liver (hypopharynx).

**Conclusions:** These results suggest that the triple regimen is more effective than the standard protocol especially in view of the high rates of complete remission. More detailed results of this organ preservation protocol will be presented at the meeting.

### Results of salvage surgery for local or regional recurrence after larynx preservation with induction chemotherapy and radiotherapy.

X. Leon, C. Orus, MP. Venegas, M. Quer (Barcelona, Spain)

**Background:** After treatment of locally advanced laryngeal carcinomas with induction chemotherapy and radiotherapy some patients suffer a local or regional failure of the tumor and salvage surgery is required. The aim of this study was to review the results of such salvage surgery in this group of patients

**Methods:** A retrospective study of a cohort of 110 patients diagnosed between 1989 and 1996 with a locally advanced laryngeal carcinoma (T3-T4) treated with induction chemotherapy and radiotherapy was performed. The results of salvage surgery in patients with a local and/or regional failure of the treatment were analyzed.

**Results:** Forty-two patients presented a local and/or a regional recurrence of the tumor: 26 patients in the larynx, 8 in the neck and a further 8 in both in the larynx and the neck. Salvage surgery was carried out in 28 patients (67%), consisting of total laryngectomies with neck dissections (24 cases), endoscopic resection of the tumor

(one case) and radical neck dissections (3 cases). Five-year adjusted survival for the 42 patients was 38%. Five-year survival for the 28 patients treated with salvage surgery was 57%. Five patients had postoperative complications: four pharyngo-cutaneous fistulas and one wound infection.

**Conclusions:** After a local and/or regional recurrence, 67% of patients with advanced laryngeal carcinoma treated with induction chemotherapy and radiotherapy were candidates to salvage surgery. Five-year adjusted survival for this group of patients was 57%.

### Interstitial photodynamic therapy as salvage treatment for recurrent Head and Neck cancer

PJ. Lou, HR. Jäge, L. Jones, T. Theodossy, SG. Brown, C. Hopper (London, United Kingdom)

**Background:** The management of recurrent head-and-neck cancers with present treatment modalities carry significant morbidity and mortality without improving the survival. Photodynamic therapy (PDT) has been shown in recent studies to be safe and effective in the treatment of pre-malignant and malignant lesions. The current limitation of PDT is the depth of tissue injury. To overcome this limitation, we used interstitial PDT (IPDT) and conducted the first phase I-II study in recurrent unresectable head-and-neck cancers. The aim of this study was to assess the safety of IPDT for recurrent head and neck cancers.

**Methods:** 45 patients were treated in a multidisciplinary oncology clinic at the University College London Hospitals and the follow up was available on 39.

**Results:** Nine achieved a complete response of whom five are alive and free of disease 10-60 months later. Symptomatic relief (mainly for bleeding, pain or tumour debulking) was achieved in a further 23. Overall median survival (Kaplan-Meier) was 14 months. The median survival was 16 months for the 32 responders but only 1 month for the seven non-responders. The only serious complication was a carotid blow out 2 weeks after PDT.

**Conclusions:** IPDT provides worthwhile palliation with few complications and occasional long term survivors for otherwise untreatable advanced head and neck cancers. It is a treatment option worth adding to those available to integrated head and neck oncology teams.

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## Posters

### Angiogenesis and cervical lymph node metastasis in oral squamous cell carcinoma

J. Beck Mannagetta, R. Sedivy, C. Haverkamp, W. Battistutti, S. Hoenigschnabl (Salzburg, Austria)

**Background:** It has long been suspected that the density of blood/lymphatic microvessels within oral squamous cell carcinoma (OSCC) is responsible for the mode of metastatic behaviour. However, until recently a clear morphologic distinction between the two types of vascular capillaries was not possible. The recently developed antibody against podoplanin makes possible the visualisation of lymphatic microvessels versus blood microvessels. In this study we tried not only to correlate the density of blood and lymphatic microvessels in relation to VEGF-C but also to compare these findings with the metastatic behaviour and clinical long-term results in our patients.

**Methods:** The expression of VEGF-C as well as the density of lymphatic (LVD) and blood microvessels (MVD) were determined by antibodies against podoplanin and CD34. These findings were compared with the clinical data of 28 patients.

**Results:** Lymphatic microvessel density correlated with VEGF-C, tumor grade, nodal status and later metastasis. The latter three parameters had no influence on the clinical course of the disease. Intratumoral LVD and MVD were significantly higher than in control tissues.

**Conclusions:** VEGF-C expression in OSCC induces lymphatic angiogenesis, which may result in a higher risk for cervical lymph node metastasis. Due to the small number of patients we suggest a prospective study in a larger group in order to arrive at statistically significant conclusions.

### The use of the navigator in head and neck oncology: real or virtual

R. Cocchi, MG. Pennesi, F. Neri, L. Lancellotti (Bologna, Italy)

**Background:** The navigator is an instrument which allows the use of CT and NMR imaging during surgical procedures. Specific instruments allow us to know the exact position of the operator. After the pioneering work of Kelly in the 80's some companies began producing it and it was introduced in Europe at the beginning of 90's. Its use has two principal objectives:

1. Programming of the optimal surgical access route.
2. Evaluation of the exact anatomical position of the instrument of the operator in order to point out structures of particular interest.

**Methods:** The neuronavigator was introduced in Bellaria Hospital by neurosurgeons four years ago. Daily collaboration induced us to evaluate its use in our discipline. Its use requires CT or NMR imaging pre-operatively according to standard protocols. These images, re-elaborated, are visualized during the operation and are used with special instrumentation. We have been using it for the past few months in patients having mid-third region tumors due to its topographic complexity. Of four patients, 3 had malignant neoplasias and one had an ameloblastoma.

**Conclusions:** We have made the following judgments: easy and precise identification of important structures useful as anatomic findings; evaluation of the distance of the neoplasia during surgical maneuvers; identification of the best route of access in performing an osteotomy. We therefore hope to develop software specific to Maxillo-Facial Surgery.

### The influence of the pattern of mandibular invasion on recurrence and survival in oral squamous cell carcinoma

J. Brown, R. Shaw, J. Woolgar (Liverpool, United Kingdom)

**Background:** There is controversy over the predictive value of the presence and pattern of tumour invasion of the mandible in oral SCC. Many authors have questioned the upstaging of small tumours to T4 on the basis of mandibular invasion alone. There is very little data on the influence of the invasive pattern on prognosis.

**Methods:** Prospective review of 100 consecutive mandibular resections for previously untreated oral SCC. Clinical and pathological data collected included details of soft and hard tissue histology. Outcomes included recurrence (local, regional and distant metastases), disease specific survival and death due to other causes. Median follow-up for survivors was 65 months.

**Results:** Of 100 cases, 65 were segmental and 35 were marginal resections. 62% of mandibles were invaded by tumour. Local recurrence occurred in 21% and was strongly correlated with tumour size, nodal involvement and soft tissue invasive pattern. Mandibular invasion predicted for recurrence, and even after correcting for the effects of other variables. The pattern of mandibular invasion (erosive/infiltrative) was also predictive for recurrence. Five year disease specific survival was 68% and crude survival was 50%. Tumour size, soft tissue invasive pattern, presence and pattern of mandibular invasion correlated with disease specific survival.

**Conclusions:** Even in the presence of mandibular invasion, soft tissue factors are the most important determinants of prognosis. Upstaging tumours on the basis of mandibular invasion may be justified. An infiltrative pattern of bone invasion is a marker of aggressive tumour biology but its role in staging is not proven.

### Elastic Light Scattering: bloodless biopsies and instant pathology

W. Jerjes, D. Pickard, B. Swinson, G. Thomas, C. Hopper  
(London, United Kingdom)

**Background:** While histopathology remains the gold standard for tissue diagnosis, several new diagnostic techniques are being developed that rely on physical and biochemical changes that precede and mirror malignant change within tissue. The technique involves the use of Mie effect and is a simple non-invasive method of tissue interrogation. The aim of this study was to compare findings of Elastic Light Scattering with histopathology on formaline fixed neck dissection specimens and to see if this technique could be used as an adjunct or alternative to histopathology in defining nodal involvement in neck dissection surgery.

**Methods:** 130 lymph nodes were examined from 12 patients who underwent neck dissections. The nodes were bi-valved subject to Elastic Light Scattering and then went on to formal histopathological investigation. The probe is momentarily placed over the bi-valved lymph node and the system is activated. The latter consists of a pulsed, xenon-arc lamp light source, a PC-compatible spectrometer and a fibre optic probe. An ESS reading is generated by subtracting a background reading from a pulsed xenon-lamp reading. This signal shows greater intensities in malignant nodes than in non-affected ones when analysed through a computer program.

**Results:** 299 negative and 48 positive nodes were encountered. The intensity of the spectra at 4 points was considered for comparison, at 360nm, 450nm, 630nm and 690nm. This showed that it is possible to obtain a: Sensitivity of 98%, Specificity of 67%

**Conclusions:** Elastic Light Scattering is a quick, accurate way of examining pathological tissue. The accuracy found in this study, suggests that it could save time and money in histopathology laboratory.

### Different expression of Cox-II in follicular cancer and follicular adenoma of the thyroid

Y. Suh, CS. Chun, HM. Chin, HM. Cho, JG. Kim, WB. Park  
(Suwon, Korea)

**Background:** Until now, it is not possible to distinguish follicular adenoma from follicular cancer of the thyroid gland preoperatively. We tried to know whether the expression of the cyclooxygenase II (COX II) detected by the immunohistochemical (IHC) staining of the pathologic specimen is different in intensity between adenoma and carcinoma. If it is so, we want to know that it can be used as a distinctive feature for either one.

**Methods:** Study population was 15 follicular adenomas and 15 follicular cancers of the thyroid glands. They underwent lobectomy or more between January 1998 and December 2002. We used Zymed® kit for COX II IHC staining. The intensity per se was neglected for the evaluation of the staining intensity.

**Results:** Though the study population was so small to conclude from our results, but we can see the difference between two groups. In 11 of 15 carcinoma cases, inflammatory reaction with numerous leukocytes was easily found and the IHC staining intensity of COX II was relatively strong than those of the adenoma. Unfortunately 4 of 15 cases of follicular cancer, we cannot see any difference compared to adenoma group. Only 2 of cancer and 3 of adenoma cases were male, so we can't calculate sexual difference with the results.

**Conclusions:** Though this experiment was kind of a pilot test for the future studies, but we think that it is worthy of more study for the COX II expression in follicular adenoma and carcinoma of the thyroid. And if someone can prove its clinical efficacy as a distinctive measure, we possibly can go beyond the results to adopt its usage to fine needle aspiration cytology.

### Cox-1 expression is upregulated in head and neck squamous cell carcinoma

BM. Erovic, C. Neuchrist, M. Grasl, D. Turhani, D. Thurnher  
(Vienna, Austria)

**Background:** Previous studies showed that cyclooxygenase-1 is constitutively expressed as a housekeeping enzyme in most tissues whereas cyclooxygenase-2 is induced during inflammatory processes, carcinogenesis and angiogenesis. We investigated whether Cox-1 has housekeeping gene function and is possibly connected with flk-1 expression, a VEGF receptor, in head and neck carcinomas.

**Methods:** Immunohistochemistry was performed in 41 paraffin-embedded tumor specimens and 6 specimens of normal oral mucosa.

**Results:** Cox-1 was upregulated in all tumor specimens compared to normal mucosa. The expression pattern of Cox-1 and Cox-2 compared to flk-1 was nearly identical in 33 (72%) and 36 (79%) of 46 tissue biopsies, respectively. Cox-1 and Cox-2 demonstrated the same enhancement in 37% of all tumor samples. Western Blot analysis confirmed the immunohistochemistry results showing that Cox-1 is upregulated in tumor specimens compared to normal oral mucosa.

**Conclusions:** Our findings support the hypothesis that Cox-1 as well as Cox-2 is an inducible enzyme in head and neck squamous cell carcinoma. Thus both enzymes may be of importance for the linkage between chronic inflammation and carcinogenesis as well as angiogenesis and subsequently tumor outgrowth.

### Ki67, cyclin D1 and p53 in the squamous cell carcinoma of head and neck

P. Golusinski, J. Stanczak, J. Klosin, W. Golusinski  
(Poznan, Poland)

**Background:** The difficult and complicated mechanism of cancer development on one hand, and the insufficient knowledge of the biology of the established cancers on the other have led to a constant search for new techniques of diagnosis in order to better evaluate and to improve the overall prognosis in patients and selection of the most efficient methods of treatment. The aim of the study was to analyze the selected prognostic factors such as i.e. p53, Ki67 and cyclin D1, in patients with head and neck cancer in connection with histological differentiation (G), TNM classification and the clinical advancement of the disease (S).

**Methods:** The material comprised the tissue specimens from 32 patients with squamous cell carcinomas of head and neck who underwent primary surgery. The clinical data concerning sex, age, site and extent of the tumor, treatment, histopathological differentiation (G), and TNM classification and advancement of the disease (S) were recorded and analyzed. The histopathological differentiation of the tumors was done on the hematoxylin-eosin stained sections. Immunohistochemical study was performed with the avidin-biotin method. A 5-point grading system was adopted to assess the level of immunohistochemical staining of the carcinoma cells.

**Results:** Through our study we found a statistically significant correlation between the staining intensity of carcinoma cells for p53, Ki67 and cyclin D1 and the TNM classification and the clinical advancement of the disease (S). However, nevertheless such correlation between staining intensity for mentioned factors and histopathological differentiation (G), has not been observed.

**Conclusions:** The traditional parameters such as histopathological differentiation (G), TNM classification and clinical advancement of the disease (S), should not be the only factors of evaluation of the biology of squamous cell carcinomas. The immunohistochemical techniques may constitute an important supplement of evaluation of the malignancy in squamous cell carcinomas of head and neck.

### Evaluation of laminin expression in patients with neck metastases in squamous cell carcinoma of the larynx

D. Mielcarek-Kuchta, J. Olofsson, W. Goluszinski (Poznan, Poland and Bergen, Norway)

**Background:** The aim of the study was to assess the importance of the laminin expression in relation to metastases in the neck nodes in patients with laryngeal carcinoma.

**Methods:** The study comprised 70 patients with squamous cell carcinoma of the larynx treated in the ENT Department, University of Medical Sciences in Poznań. The clinical data concerned: sex, age, stage of the tumor, histological examination and immunohistochemistry. The average follow-up time was 3 years. The immunohistochemical examinations were performed using sections of formalin fixed and paraffin embedded tissue containing tumor. Monoclonal antibodies from DAKO were used for immunohistochemistry. A four-point grading system were used to evaluate the laminin staining: score 0-continuous, score 1-loss of staining less than 10%, score 2- loss of staining less than 50%, score 3- loss of staining more than 50%. The correlation between the staining intensity of the laminin and occurrence of the neck metastases (classified as N-positiv and N-negativ necks) was examined. All parameters underwent statistical analysis.

**Results:** The patients with advanced clinical disease dominated in our material. Most of the tumors were classified as T3 and T4. 36 patients had metastases to the regional lymph nodes. A positive laminin staining was observed in 62 cases (30 with positive nodes and 32 with negative nodes). No correlation was found between laminin staining and occurrence of neck metastases. However there was a statistically significant correlation within the group with metastases and a positive laminin staining (30 patients) showing a higher rate of regional recurrence in the high scoring-laminin group (Wilcoxon test,  $p=0.00044$ ).

**Conclusions:** It seems that the more marked the laminin loss the higher is the the risk of neck failure.

### Reevaluation of the pharmacological microheterogeneity of head and neck squamous cell carcinoma in ex vivo chemosensitivity tests

R. Dollner, A. Rueb, C. Granzow, A. Dietz (Heidelberg, Germany)

**Background:** Since *in vitro* chemosensitivity tests uses single biopsies to characterize entire tumors pharmacologically, previous studies on the tumors microheterogeneity resulted in fundamental criticism regarding the plausibility of such tests. Recently, flavin-mediated photochemical reactions were identified in cell culture systems which mimic significant pharmacological differences. Using appropriate methods to avoid these artifacts seem mandatory to investigate the actual existence and role of the pharmacological heterogeneity in solid tumors. Using a novel *ex vivo* protocol based on flavin-protecting culture conditions, we investigated, whether a single biopsy can be pharmacologically representative for a given head and neck tumor.

**Methods:** Parallel *ex vivo* colony formation tests were done with separate biopsies from three distinct locations of eleven HNSCC primary tumors. Explant digests were exposed to concentration gradients containing: carboplatin, cisplatin, 5-fluorouracil, docetaxel, and glufosfamide. The concentration gradients covered the respective IC50 of KB cells (ATCC), as well as the clinically achievable drug concentration. Drug concentrations required to completely suppress tumor cell colony formation were identified microscopically.

**Results:** Using an improved test protocol, the extent of previously encountered major pharmacological microheterogeneity of solid tumors could not be confirmed. Comparison of the chemosensitivity profiles for the different biopsies from each of the tested tumors showed fewer differences as described in previous studies. The individual responsiveness to the five tested drugs differed strongly.

**Conclusions:** Our findings indicate that appropriate methodical

precautions in chemosensitivity testing may allow for predicting the responsiveness of a given tumor by analyzing a single biopsy.

### Application of cell lines in cytogenetic studies of laryngeal cancer

W. Goluszinski, M. Jarmuz, R. Grenman, M. Kujawski, K. Szyfter (Poznan, Poland and Turku, Finland)

**Background:** An introduction of molecular techniques to cytogenetics has considerably extended its potential and interpretation of chromosome alterations. The aim of the study was to analyse chromosome aberrations in relation to progression of laryngeal cancer. **Methods:** A panel of 16 established cell lines representing a variety of tumour characteristics concerning staging and histology grading was analysed by conventional cytogenetics, comparative genomic hybridization (CGH) and fluorescent in situ hybridization (FISH).

**Results:** The most frequent aberration was a loss of chromosome Y followed by aberration of autosomes 1, 2, 3, 5,7, 8, 9, 11 and 18. Particularly, deletion of 9p, 3p and 18q, amplifications 3q, 8q and 11q13 seem to be associated with pathogenesis in laryngeal cancer. Also frequent breaks in centromeric and pericentromeric regions appear to be linked to laryngeal cancer initiation and progression. Amplification of 11q13 region, already recognized as a marker of poor prognosis should be estimated together with amplification of 3q arm or with other aberrations within 11q13. We have not found any specificity of chromosome aberrations related to histologic grading.

**Conclusions:** The results indicate that a combination of conventional and molecular cytogenetic techniques provides a useful tool as diagnostic and prognostic marker.

### Telomerase Inhibition with AZT radiosensitises head and neck cancer cells

J. Mc Caul, EK. Parkinson (Glasgow, United Kingdom)

**Background:** Telomerase is a new, potentially highly selective cancer therapeutic target. Telomeres at the chromosome ends shorten with cell replication. The immortalisation of human cancer cells requires maintenance of these telomeres through many rounds of replication. In more than 90% of all human tumours this is achieved by the upregulation of the telomerase enzyme; a RNA dependent reverse transcriptase. In epithelial cancers, including squamous carcinoma of the head and neck, the percentage of tumours utilising this mechanism may be even higher. This distinction between normal and malignant cells represents an attractive target for new, more specific anticancer therapies. The telomere has many functions and associated proteins including those involved in repair of DNA double strand breaks (DSB). The DSB is the lethal cellular injury produced by ionising radiation. The aim of this study was to investigate whether telomerase inhibition, producing telomere shortening and/or dysfunction affects the radiosensitivity of cancer cells

**Methods:** We have increased telomerase levels in cancer cell lines derived from *in vivo* human squamous cancers by stable transfection of the hTERT gene and assessed radiation survival. We further describe experimental data from work using the reverse transcriptase inhibitor AZT (3'-azido-deoxythymidine) to inhibit the telomerase enzyme in human oral squamous carcinoma cells.

**Results:** In cells with low endogenous telomerase increasing expression produced radioprotection. Where telomerase inhibition was achieved with AZT (assayed using the TRAP PCR method) corresponding SF2 (surviving fraction after two Grays of radiation) was reduced.

**Conclusions:** Telomerase inhibition acts synergistically with ionising radiation in head and neck squamous cancer cell lines.

### Quality of life after radical surgery and radiotherapy for advanced laryngeal and hypopharyngeal cancers

A. Dequanter, P. Lothaire, D. Eeckout, M. Colin, M. Comblain, G. Andry (Brussels, Belgium)

**Aim:** To determine the functional disabilities and overall quality of life of patients operated for advanced (Stages III - IV) or recurrent squamous cell carcinomas (SCCA) after radiation therapy of the pharyngolarynx.

**Methods:** From 1984 to 1997, 135 patients were consecutively treated for SCCA of the pharyngolarynx. There were 118 men and 17 women with a mean age of 60 years. The University of Washington QOL questionnaire (UW-QOL) (Deleyiannis & al., Head and Neck, 1999) was administered to 19 long term survivors. Self-administered scale consisting of nine domains affected by treatment for head and neck cancer: pain, physical appearance, global activity, entertainment, employment, chewing, swallowing, speech and shoulder function. For each patient, a total score and a weighted score (sum of the products score and weight, divided by the sum of the weighted scores) were determined. Descriptive statistics were used.

**Results:** 9/19 patients reported that compared with one year prior to the diagnosis of cancer their general health was the same or better. Pain resolved in 78 % (table I); the physical appearance was judged « not modified » in 52 % of the cases (table II). Chewing and swallowing functions were respected in 94 % of the cases (table III & IV). These functions were considered as very important in 53 % and 68 % respectively (table V & VI). 5 patients are still at work; 11 patients retired. Work was considered as very important for 9/19 patients. Speech rehabilitation permitted a modified but well understandable communication in 63 % of the cases. This function was considered by 88 % of the patients as very important (table VII). Finally, 73 % of the patients (14/19) reported having a good to excellent overall QOL (table VIII).

**Conclusion:** Though disabling, pharyngolaryngectomies do not necessarily translate into a worse overall QOL: ultimate disabilities are widely variable. Many factors such as family, friends personal leisure activities, employment cultural habits were important and depending on each patient in the enjoyment of life's estimation.

### Percutaneous endoscopic gastrostomy in head and neck cancer patients

R. Grenman, K. Hujala, J. Pulkkinen, J. Sipila (Turku, Finland)

**Background:** Poor nutrition in head and neck cancer patients before, during and after treatment with curative intent is a significant problem. With the use of extensive surgery including reconstructions, intensified (chemo) radiotherapy and their combination the need for assisted enteral feeding is obvious.

**Methods:** In 1999-2001 80 recently diagnosed HNSCC patients were treated with 85 percutaneous gastrostomies (PEG) by us in the ENT Department. The mean age of the 64 male and 16 female patients was 64.4 years (range 30-92 y). The PEG was introduced electively in 92.5%. The PEG (Flocare no 14™, Nutricia) was installed in local anaesthesia (78.5%) or in general anaesthesia in connection with other procedures such as panendoscopy, tracheostomy, new biopsies or dilatation of esophageal stricture. In 6 six cases an open gastrostomy was needed due to severe oesophageal stricture (n=5) or severe trismus (n=1).

**Results:** The PEG was the main source of alimentation in 27 patients (33.8%), a valuable part of the nutrition for 6 over months (23.8%) or assisting the nutrition especially during the treatment and immediate recovery in 23 (28.9%) cases. No severe complications occurred and the minor complications were: eructation and leakage of air into the free abdomen (n=1), local infection (n=3), ablation of the catheter (n=3), leakage (n=3), breaking of the catheter (n=1), fistula and abscess of the abdominal wall (n=1). In case of catheter problems a new catheter was reinstalled instantly. The infection problems were treated successfully with antibiotic therapy and only the localized abscess required minor surgical draining.

**Conclusions:** Based on this experience PEG installed by ENT-specialists continuous to be a routine procedure in HNSCC patients requiring combined modality or extensive single modality treatment in our department.

### Organ preservation surgery for advanced laryngeal carcinoma: our attitude

JC Pignat, M. Poupard, B. Navailles, JP. Texier, A. Cosmidis, M. Robert (Lyon, France)

**Background:** Protocols of chemotherapy used to preserve the organ in advanced laryngeal carcinomas raise the question of the attitude to have concerning partial responders representing the largest number of patients. The aim of this retrospective study is to show oncologic and functional results of partial surgery in advanced cancers.

**Methods:** Thirty-seven patients (28 T3, 9 T4) have been treated with partial laryngeal surgery. Concerning N stage, 27 were N0, 7 N1 and 3 N2. Eight patients had been treated before by neoadjuvant chemotherapy. The surgery performed was 14 supraglottic laryngectomies and 23 supracricoid laryngectomies. The selection of eligible patients and the indications are notified. Postoperative radiotherapy was delivered in 32 patients (4 to the tumoral site only, 28 to the tumoral site and to the nodal areas).

**Results:** No postoperative death has been reported. Twenty-six patients have been tracheotomized, decannulation was done in an average of 41 days (13 days when the decannulation was done before radiotherapy). The nasogastric tube was removed on average on the 47th day. The average hospitalization was 29 days. Four patients kept permanent tracheotomy, one kept permanent gastrostomy. No completion total laryngectomy has been performed. The laryngeal preservation rate was 86.5% (100% when permanent tracheotomy and/or gastrostomy are included). The one-year survival rate was 81.1 %, the 3-year survival 54.8% and the 5-year survival 44.9%.

**Conclusions:** Partial laryngeal surgery with postoperative radiation in T3- T4laryngeal cancers applied to selected patients allows laryngeal preservation with similar survival rates to total laryngectomy.

### Partial laryngectomy and carcinologic results in 356 laryngeal cancers

V. Strunski, S. Ayache, C. Page, J. Peng, N. Raverdy, A. Dubreuil (Amiens, France)

**Background:** The aim of this study was to define the proportion of partial surgery and the survival rate in a population with laryngeal cancers.

**Methods:** statistic method with chi 2 analysis after information collection in hospital and town registers.

**Results:** From 1987 to 1997 the Cancer Register of the french department of Somme listed 356 laryngeal cancers; 76% of them were treated in the University Hospital of Amiens. The first checking metastas were discovered in 5.8% of cases and a second cancer in 3.4%. During the follow up metastases appeared in 9.8% of cases and a second cancer in 5%. 61% were treated through surgery (exclusively in 20.8%), radiotherapy in 72% (exclusively in 18%) and chemotherapy in 29%. Partial surgery was performed in 29.5% of cases and subtotalaryngectomy in 16.5%, total laryngectomy in 53%. The first stage cases of cancers (79) were treated through surgery in 58% with a five year survival rate of 90% and in 42% through radiotherapy with a survival rate of 58.6%. The second stage cases of laryngeal cancers (106) were treated through surgery in 66% of cases with a survival rate of 79% and through radiotherapy in 34% with the survival rate of 27%.

**Conclusions:** The more frequently performed treatment in this series for the first and second stages of laryngeal cancer was partial surgery rather than radiotherapy.

### A successful interdisciplinary approach: treatment of head & neck tumours in the head & neck oncology center

BS. Lutz, L. Löfgren, R. Adell, J. Reizenstein (Orebro, Sweden)

**Background:** The Head & Neck Oncology Center is an institution dedicated to the diagnosis and treatment of head & neck tumours. The center is based on a close collaboration between several departments (Oncology, BNT, Oral and Maxillo-facial Surgery, Plastic Surgery) with formal tumor board meetings. Additionally, lectures, teaching of residents and nurses, and conferences are regular activities in the Center.

**Methods:** Each patient is given a comprehensive work-up. The basis diagnosis and treatment is evidence based medicine. When eligible, patients are included in clinical trials after informed consent. Treatment modalities are offered without unmotivated bias towards specific modalities (radiotherapy, surgery, brachytherapy, etc). The selected treatment form is proposed to the patients after consensus at the tumor board meeting. Usually, the BNT-surgeons -and the oral and maxillo-facial surgeons in case of bone involvement -are responsible for the tumour resections. The reconstruction is decided by the plastic surgeon according to the patient's general health situation and to the needs for restoring normal function and best possible esthetic outcome. Secondary treatment (i.e. irradiation) and secondary rehabilitation (i.e. dental implants) are performed in the respective departments. All patients are followed-up for a minimum of 5 years.

**Conclusions:** Approximately 85 major head & neck reconstructions have been performed since March 2000. The presented collaboration has proven to be an excellent method for treating patients with tumours in the head & neck area aiming at a high cure rate, restoring normal function and acceptable aesthetic results, combined with a low morbidity rate and optimized costs.

### Guidelines for the selection of the Clinical Target Volumes in pharyngo-laryngeal squamous cell carcinoma treated by Three-dimension Conformal Radiotherapy or Intensity Modulated Radiation Therapy

V. Gregoire, JF. Daisne, X. Geets, M. Hamoir, H. Reyckler (Brussels, Belgium)

**Background:** The exquisite dose distribution which can be obtained with 3D-CRT and IMRT requires a very precise and reproducible selection of the target volumes for both the primary tumor and the neck nodes. The Clinical Target Volume (CTV) encompasses both the macroscopic tumor that can be visualized by clinical and/or radiological (i.e. CT or MRI) examination, but also the microscopic tumor extension. Guidelines for the selection and the delineation of the neck node levels have been already published by our group (Radiother. Oncol., 56: 135-150, 2000). Such guidelines

do not exist for the primary tumors, but could be elaborated based on the general principles that the microscopic spread of SCC follows anatomical compartments (e.g. para-laryngeal, para-pharyngeal, pre-epiglottic spaces) bounded by anatomical barriers (e.g. bone cortex, muscular fascia, ligaments). Unless transgressed, such barriers would limit the local primary tumor spread. The objective was to elaborate comprehensive recommendations to be used for 3D-CRT or IMRT for the selection of the CTV of pharyngo-laryngeal SCC as a function of the location and extension of the macroscopic tumor.

**Methods:** A comprehensive review of the pathological literature was performed to assess the microscopic spread of SCC of the larynx (sub-glottis, glottis and supraglottis), hypopharynx (piriform sinus, retrocricoid area, posterior pharyngeal wall) and oropharynx (base of tongue, tonsillar fossa, soft palate, posterior pharyngeal wall). When necessary, boundaries for the CTV were adjusted to take into account the anatomical resolution of the imaging modalities (i.e. CT, MRI) used for the planning purpose.

**Results:** An example of the recommendations for the CTV in hypopharyngeal SCC is presented in the following table.\*

**Conclusions:** These recommendations should facilitate homogeneous selection and consequent delineation of CTV for pharyngo-laryngeal SCC. They should also contribute to a decrease of the radiation dose to non-target tissues, possibly allowing dose escalation and/or reduction in treatment morbidity.

### Concomitant chemoradiotherapy in locally advanced Head & neck cancers - early results

N. Jain, R. Devgan, AK. Bhatia, GS. Brar, A. Singh, US. Dhaliwal (Amritsar, India)

**Background:** Prevalance of head & neck cancers is high in developing world. This is attributable to poverty, poor orodental hygiene and tobacco chewing. These factors also contribute to late and advanced presentations. Surgery is out of question in this setting and Radiation alone fails to achieve satisfactory local control. With the aim of achieving better local control and a better quality of life chemoradiation was given to these patients.

**Methods:** From April 2001 to April 2002, 21 patients of locally advanced head & neck cancers were studied. None had distant metastasis. All had squamous cell carcinoma histopathologically. They were subjected to External beam radiotherapy to a total dose of 66 Gy. Spinal cord sparing was done after 40 Gy. Weekly cisplatin 50 mg was given concomitantly for 6 weeks. CBC and serum creatinine levels were checked before each dose.

**Results:** 19 patients completed the treatment and were evaluable. 14 (75%) achieved complete response and 4 partial response and 1 stable disease as per criteria laid down by World Health organisation. Toxicities were low grade and were manageable. There were 2 late recurrences.

\*

Anatomic structure	Piriform sinus (PS)	Retrocricoid area (RC)	Posterior pharyngeal wall (PW)
Mucosa	Entire PS	Entire RC	Entire PW
Ary-epiglottic fold	Ipsi-/bilat according to CTV extension	Ipsi-/bilat according to CTV extension	In case of PS or RC invasion
Para-glottic space	Ipsilateral	In case of PS invasion	In case of PS invasion
Thyroid cartilage	Macroscopic infiltr; paraglottic space infiltr : lateral wall infiltr.	See recom. for PS	See recom. for PS
Posterior pharyngeal wall	Lateral wall and/or PW infiltration	No	Always included
Inter-arytenoid muscles	If RC infiltration	Always included	No
Longus capiti muscles	No	No	Direct infiltration
Vocal cord	Para-glottic space invasion/direct infiltration	Ipsilateral	No
Cricoid cartilage	Se RC	Direct invasion and/or arytenoid infiltration	See RC
Pharyngeal fat	Direct infiltration	No	Direct infiltration

**Conclusions:** Chemoradiation is ideal mode of treatment in locally advanced head and neck cancers. Cisplatin is the drug of choice in this setting being economical, easily available and administerable in Outdoor settings when used in low doses.

#### **Weekly paclitaxel in patients in recurrent and/or metastatic head and neck squamous cell carcinoma.**

Z. Merad Boudia, A. Marti, JP. Camuzet, A. Sharif, A. Le Tarnec, E. Chopineau, T. Tournay (Boulogne sur Mer, France)

**Background:** The aim of this study was to assess the efficacy and the toxicity of weekly paclitaxel in patients (pts) with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC). Even if Methotrexat is currently used in second line there is no efficient chemotherapy and pts who failed to the standard first line 5FU-Cisplatin chemotherapy have poor prognosis survival. Monthly paclitaxel is an active and interesting drug in several solid tumors and weekly paclitaxel seems less toxic and probably more efficient than monthly paclitaxel (possibly because of the proapoptotic and anti-angiogenic activity), the dose-intensity is quit higher and the toxicities are mild.

**Methods:** Ten recurrent and/or metastatic HNSCC pts with PS: 0 to 2, all previously pretreated with the standard 5FU-Cisplatin regimen and/or radiotherapy and/or surgery where assigned to receive paclitaxel 80 mg/sqm/week during 4 weeks every 6 weeks until documented progression or unacceptable toxicity. There were 7 males and 3 females, median age 50.7 y (range:42-72).

**Results:** Toxicity: a total of 67 cycles was administered (range 1- 27). 5 pts (50%) died, 4 of them from related toxicity: 2 pts few days after the first administration, 1 stopped because of dyspnea after 4 cycles and 1pt had a partial response >50% but developed immunologic pneumopathy after 7 months and died of progression and pneumopathy, respectively. There were no hematological or neurological toxicity. 5 pts (50%) are stable disease and are still treated.

**Conclusions:** treatment with weekly paclitaxel is feasible but it should be reserved to pts with good PS and, regarding to our non selected and small population, it should be rapidly stopped in case of any respiratory dysfunction.

#### **Methicillin Resistant Staphylococcus Aureus Infection in Head and Neck Oncological Surgery patients - An Audit.**

R. Simo, VMM. Ward, SJ. Thorne, J. Hamman, G. Gopal Rao, A. Jeannes Godstraw (London, United Kingdom)

**Background:** Methicillin Resistant Staphylococcus Aureus (MRSA) infection following head and neck surgery is a very significant cause of morbidity and mortality. MRSA infection increases the risk of wound necrosis, associated complications and prolonged hospital stay. The aim of this study was to evaluate the efficacy of a MRSA prevention and treatment protocol to reduce the incidence of MRSA infection following major head and neck surgery.

**Methods:** A retrospective audit of all patients undergoing head and neck surgery in our Unit over a period of 6 months was performed. All patients undergoing head and neck surgery whose hospital-stay exceeded 5 days were included. An analysis of the incidence, site and severity of the MRSA infection was performed. Twenty-four patients were identified in a six month period before the implementation of the protocol, 13 in the six months after and 32 patients in the second re-evaluation. The protocol consisted of screening of patients, prophylactic measures before surgery, a change in the nursing care plans and an antibiotic policy for prophylaxis and treatment.

**Results:** Twenty four patients were identified in the first limb of the audit, of these, 9 patients developed MRSA infections (37.5%). The site of MRSA infection included the lungs, tracheostomy site, surgical wound and gastrostomy site. Following the implementation of the protocol only 2 of the 13 patients identified developed

MRSA infection (15.3%). In the second re-evaluation only 4 (12.5%) patients developed MRSA infections.

**Conclusions:** The implementation of an MRSA prevention and treatment protocol has proved very effective in reducing the incidence of MRSA infection and subsequent post-operative complications following major oncological head and neck surgery.

#### **The anterior thoraco-cervical approach in advanced thyroid cancer**

P. Rhys Evans, S. Triaridis, T. Upile, P. Kirkland, P. Godstraw (London, United Kingdom)

**Background:** Advanced thyroid cancer involving the thoracic inlet and adjacent structures in the superior mediastinum can on selected cases be treated surgically but present the surgeon with a difficult problem of access.

**Methods:** A six year review of our experience using an anterior thoraco-cervical approach for resection of malignant thyroid tumours involving the superior mediastinum included 13 patients (median age 58 years). Most of these patients were either tertiary referral from other hospitals where their disease was deemed inoperable with local facilities (6 patients) or presented with local and mediastinal recurrence after previous surgery elsewhere (5 patients). They all had had widespread disease in the neck and mediastinum and most presented with severe symptoms of airodigestive tract compression.

**Results:** Complete clearance was achieved in 6 patients and macroscopic control of the disease in another 2. There were 4 complications (lung collapse, wound infection, pleural effusion). On follow up 5 patients were alive with no signs of recurrence, 3 were alive with disease, 5 were dead and the median survival was 35 months.

**Conclusions:** The anterior thoraco-cervical approach in advanced thyroid cancer can achieve optimal exposure for macroscopic surgical clearance. Even when it is not possible to completely remove the tumour, reduction in tumour bulk will palliate compressive symptoms and increase the effectiveness of other treatment modalities (EBRT, I131) on residual disease.

#### **The management of cervical metastases from differentiated carcinoma of the thyroid gland.**

P. Kirkland, S. Triaridis, T. Upile, C. Harmer, P. Rhys Evans (London, United Kingdom)

**Background:** In the past the only options for the surgical treatment of cervical metastases were either simple node excision or radical neck dissection. The morbidity of radical neck dissection was found to be unacceptably high when compared to "cherry picking". However with the advent of modern techniques of selective neck dissection with little morbidity we feel that the advantages of this technique outweigh those of simple node excision.

**Methods:** A sixteen-year review of 75 patients, all with N1 and 8 with M1 disease, who underwent selective neck dissection for the treatment of cervical metastases from differentiated thyroid carcinoma, was carried out (papillary 68, follicular 2, Hurthle 1, mixed 4).

**Results:** On follow up 62 are alive with no signs of recurrence, 8 are alive with distant metastases, 5 are dead (one of other causes) with a median follow up of 37.6 months after the neck dissection. Five patients had residual loco-regional disease on the I131 ablative scan, while two patients had recurrence in the neck. Selective neck dissection resulted in low morbidity (12% related complications).

**Conclusions:** Modern techniques of selective neck dissection have resulted in low complication rates similar to simple node picking but with the added advantages of improved staging, prognostication and reduced local recurrence rates hence overall survival. We recommend this surgical modality for the treatment of cervical metastases from differentiated thyroid carcinoma.

### Overlooked thyroid cancer: 30 to 50 years lymph node metastasis history

F. Mboti Banzene, D. Dequanter, P. Lothaire, N. De Saint-Aubain, C. Moerman, G. Andry (Brussels, Belgium)

**Aim:** Differentiated thyroid cancer (DTC) may be indolent even with lymph nodes metastases in the neck. Two patients with 30 and 50 yrs history of neck disease respectively are reported.

**Methods:** A 73 yoF referred with a 30 years history of a swelling in the right lateral aspect of the neck, considered as a benign cyst. Pain at the level of stemocleidomastoid muscle, examination: firm mass, mobile at the inferior aspect of the neck. The sonogram disclosed: 3 cm enlarged lymph node containing multiple cystic areas and a 10 mm nodule of the right thyroid lobe. Total thyroidectomy and right lymph node clearance; pathology: 2,5 cm papillary thyroid carcinoma and two involved lymph nodes. After 154,7 mCi of I131, the whole body scan (WBS) revealed one cervical residual uptake. Subsequent WBS was negative. Alive NED at 4 yrs.

A 68 yoM: history of right neck recurrent mass: operated on in 1949, histopathology revealed "a papillary cystadenoma of the thyroid" no further treatment. Referred 50 years later: enlarged neck nodes and thyroid nodule. FNA: papillary carcinoma. Total thyroidectomy with right modified neck dissection: bilateral papillary thyroid carcinoma of 1,3 cm with four involved lymph nodes. I131 administered (total dose: 617 mCi). The latest WBS was negative, Tg negative. He is NED at 4 yrs.

**Conclusion:** Overlooked DTC with longstanding cervical lymph nodes involvement didn't lead to death, no distant metastasis occurred: these highlighted the excellent long term survival with DTC.

### Positron Emission Tomography in diagnostic imaging of Head and Neck cancer. A review of the literature.

G. Regeling, J. Pruijm, A. Vissink, JLN. Roodenburg (Groningen, The Netherlands)

**Background:** The last years an increasing number of studies has been published on the potential value of Positron Emission Tomography (PET) in diagnosis and treatment evaluation of head and neck cancer. The aim of this study was to critically review the literature on the value of PET for the diagnosing, treatment monitoring and therapy planning of patients with head and neck squamous cell carcinoma.

**Methods:** Literature available in PubMed/WebSPIRS and EMBASE was selected, arranged and reviewed according to subjects of interest.

**Results:** The majority of the studies describe a heterogeneous study population. 18F-Fluoro-deoxyglucose (FDG), a glucose analogue, is the most studied radiopharmaceutical. For detection of both unknown primary tumours and recurrences, FDG-PET has become an established method reaching a higher sensitivity and in many studies also a higher specificity than computer tomography (CT) and magnetic resonance imaging (MRI). Although limited by the resolution of PET, better results for PET compared to conventional imaging are also found for cervical lymph node detection. Other applications of PET in head and neck cancer, including the use of other tracers and combined CT-PET scanning, need further study before conclusions can be drawn regarding the clinical applicability of these modalities.

**Conclusions:** It can be concluded that thus far FDG-PET has been proven to be of additional value in the detection of unknown primary tumours, recurrences and cervical lymph nodes. In this respect FDG-PET should be performed simultaneously with conventional diagnostic modalities. Further studies are needed evaluating the other applications of PET in head and neck cancer patients.

### ALA (5-aminolevulinic acid) induced protoporphyrin IX fluorescence in the endoscopic diagnostic and control of pharyngo-laryngeal cancer

M. Csanady, JG. Kiss, I. Laszlo, R. Paczona, J. Czigner, J. Jori (Szeged, Hungary)

**Background:** Photodynamic diagnostic is a modern method for the fluorescence imaging of superficial pharyngeal and laryngeal tumours. 5-aminolevulinic acid (ALA) induced IX protoporphyrin fluorescence benefits of the tumour selective accumulation of protoporphyrin; therefore tumours can be differentiated from healthy tissue. ALA induced fluorescence of laryngo-pharyngeal tumours, precancerous and benign lesions were evaluated by endoscopy.

**Methods:** At the Department of Otorhinolaryngology, Head and Neck Surgery, Szeged, Hungary 31 patients underwent ALA induced protoporphyrin fluorescence imaging. After topical application of ALA mesopharyngeal tumours were visualised by direct fluorescence endoscopy. Laryngeal and hypopharyngeal tumours were examined after inhalation of ALA solution in general anaesthesia under laryngomicroscopic view. Intensity of ALA fluorescence was classified and compared with pathological findings.

**Results:** Each examination of 13 laryngeal and 12 pharyngeal tumours resulted in middle or strong intensity of red fluorescence but one cancer, four precancerous and two benign lesions. Healthy tissues showed green autofluorescence. Margins of mesopharyngeal and vocal cord tumours were clearly seen under fluorescence vision giving a helpful contribution to the diagnostic and therapy even in clinically non-visible tumours. Laryngomicroscopy combined with laser surgery also indicated ALA fluorescence examination visualising margins of the tumour. ALA fluorescence method revealed a sensitivity of 96%.

**Conclusions:** This method is applicable for detecting early superficial tumours, margins of tumour and follow-up after surgery/radiation therapy in the laryngo-pharynx.

### MRI diagnostic accuracy in the assessment of mandibular involvement by squamous cell carcinoma: a prospective study on 43 patients

B. Bolzoni, C. Piazza, J. Cappiello, G. Peretti, R. Maroldi, D. Farina, P. Nicolai (Brescia, Italy)

**Background:** Different diagnostic techniques (orthopantomography, CT, DentaScan, scintigraphy, and SPECT) have been employed to detect mandibular invasion (MI) by squamous cell carcinoma (SCC). MRI is considered the technique of choice for treatment planning in advanced oral-oropharyngeal SCC due to its accuracy in depicting soft tissue involvement. However, growing evidences have been given about its reliability in evaluation of bony involvement too. Aims: To evaluate sensitivity, specificity, accuracy, and predictive values of MRI in the assessment of MI in oral-oropharyngeal SCC.

**Methods:** Between '94 and '03, 43 patients with untreated and/or recurrent oral-oropharyngeal SCC undergoing mandibulectomy were preoperatively examined with MRI. Indications for mandibulectomy were: MRI suggestive of bony invasion, tumor involving the retromolar trigone or the alveolar ridge, recurrent or persistent lesion, and intraoperative suspicion of periosteal invasion. Detection of tumor signal replacing the hypointense cortical rim was considered the main radiologic finding for MI. MRI findings were subsequently compared with histopathologic examination of the surgical specimens.

**Results:** 16 patients presented an MRI suggestive for MI. Segmental mandibulectomy was performed in 15 and marginal resection in the remaining 1. In 14, bony invasion was confirmed at histology. All the other 27 patients who received marginal or segmental mandibulectomy with negative MRI had no pathologic evidence of MI, except for 1 who showed, in spite of cortical integrity, neoplastic embolization into the bony lacunae, thus representing the only false negative case. Sensitivity, specificity, accuracy, negative and positive predictive values were therefore 93%, 93%, 96%, and 87.5%, respectively.

**Conclusions:** We herein demonstrate the additional diagnostic value of MRI in detecting MI. Other preoperative examinations can be considered unjustified in terms of cost and time.

**Upper aerodigestive tract squamous cell carcinoma: the distribution of extracapsular spread and soft tissue deposits in the neck**

J. Moor, J. Jose, C. Johnston, AP. Coatesworth, KA MacLennan (Leeds and York, United Kingdom)

**Background:** Extra capsular spread (ECS) and soft tissue deposits (STD) of squamous cell carcinoma (SCC) in the neck of patients with metastatic squamous cell carcinoma of the upper aerodigestive tract have been shown to adversely affect actuarial survival and disease free survival (1). No studies to date have detailed the distribution of ECS and STD within the neck or explored its clinical relevance.

**Methods:** Two hundred and fifteen neck dissections from 155 patients were prospectively collected and analysed for the presence of both STD and ECS. As no classification for STD exists, their distribution was classified according to the nodal levels used for classification of cervical lymph nodes as described by Memorial Sloane Kettering Cancer Centre.

**Results:** The distribution of lymph node metastasis, ECS and STD was very similar, level II was most frequently affected, levels III and IV were affected less frequently. Patients were grouped according to ECS or STD being present at one neck level, both ECS and STD present at one level each, or more than one level involved with ECS or STD or both. There was no statistically significant difference in survival between the 3 groups. Patients with ECS or STD at only 1 level were found to have longer median recurrence-free survival although this was only of marginal statistical significance ( $p=0.04$ ).

**Conclusions:** The method of pathological assessment of neck dissection specimens and reporting on the presence ECS and STD has not been formalised. By analysing the neck dissection specimen in the manner we describe we can report on the presence or absence of ECS and STD with increased accuracy. This has considerable implications for patient management.

**Funding:** This work has been carried out with financial assistance from The Head & Neck Research Fund, Leeds Teaching Hospitals NHS Trust and Cancer Research UK.

**Conflicting interests:** None declared

**Cancer of maxillary sinus: a retrospective study of 22 cases.**

O. Malard, C. Bignoumba, F. Jegoux, E. Bardet, F. Rolland, C. Beauvillain de Montreuil (Nantes, France)

**Background:** Cancers of the maxillary sinuses are unusual and their histological properties are very variable. These tumours may either have occasionally a metastatic origin or, more often, a maxillary mucosal or mesenchymal origin. The tumour extension in deep anatomical areas provides non specific and late warning signs. Thus, treatment is likely initiated for very advanced stages. Prognosis is at a low level, due to the local growth, and depends on the possibilities of local removal of the tumour. Modern imaging has improved the pre therapeutic approach regarding to skull base, infra-temporal and ocular involvement.

**Methods:** This retrospective study of 22 cases was performed during the last 13 years in the University Hospital of Nantes, France. Authors describe the histological data, the TNM stage, the local extension, and the therapeutic management (surgical approach, radiation therapy and chemotherapy deliveries). The long-term quality of life was assessed by a retrospective sent opinion poll following the treatments.

**Results:** Survival statistical analysis (Kaplan-Meyer) was 63.3% at 12 months and 24.1% at 24 months and 16.1% after 5 years. The specific survival is defined according to histological characteristics, TNM stage, quality of the tumour resection and scheduling of radiation therapy start.

**De-centralised data collection in Head and Neck Cancer – Experience of the Liverpool Head and Neck Cancer Database User Group 1995 – 2003.**

P. Magennis, S. Rogers, C. Leitner (Liverpool, United Kingdom)

**Background:** The importance of collecting of data on cancer patients goes beyond the need for good clinical records. However, the philosophy of the users of the Liverpool Head and Neck Cancer Database (LHNCD) has always been that the data must be available at the chair side, so that it is an adjunct to the clinical notes. This contrasts to the more centrally based systems where paper proformas are collected and processed centrally such as DÖSAK. The other principle was that the key data is always presented to the clinician at each visit, providing a reminder of the clinical details and regular validation of the data recorded.

**Methods:** Between 1995 and 2003 the LHNCD has been available for use by clinicians involved in the management of head and neck cancer. The software, cost and method of distribution has changed (it is now available on the British Association of Oral and Maxillofacial Surgeons website [www.baoms.org.uk](http://www.baoms.org.uk) rather than on a disk) but the stress on the importance of data collection by clinicians beside the patient has remained the same. As the value of quality of life instruments was recognised, the ability to record the University of Washington QOL V4 was added.

**Results:** Users of the LHNCD currently have recorded details of over 7000 patients with head and neck pathology. Most users are in the United Kingdom with clinicians in Belgium and Holland using this version in English. A new German Language version is gaining popularity in Germany. A summary of the data available will be presented, along with illustrations of the results of analysis of pooled data, including disease specific mortality (62% at 5 years) for the United Kingdom group.

**Conclusions:** De-centralised data collection using a database designed to supplement clinical records, can generate useful and interesting results.

**Verrucous cancers in head and neck; a 10 year material**

P. Homoe, C. Lajer (Copenhagen, Denmark)

**Background:** Verrucous cancer in head and neck areas represents a problem both diagnostically but also by choice of treatment. The dilemma is whether this low grade cancer type is best treated by surgery, radiotherapy or combination therapy.

**Methods:** We have performed a retrospective analysis of all cases registered at our Department of Pathology with the histological diagnosis verrucous carcinoma in the oral cavity and larynx. Our centre covers a population of approx. 1.8 million people in eastern Denmark, The Faroe Islands and Greenland. We have investigated epidemiological data, treatment modalities and outcome Patient characteristics: In total we have registered 19 patients with histologically verified verrucous carcinoma. Medical records exist in 16 patients. Fourteen cancers were situated in the oral cavity predominantly in gingival and buccal mucosae and two were laryngeal cancers. Nine were males and seven were females. The age distribution ranged from 12 to 84 years at diagnosis with a median age of 66 years.

**Results:** The tumor size varied considerably. Five had only surgery, two only irradiation and nine had combination therapy. Nine patients had recurrences with a range of seven months to 10 years, median two years. The seven recurrence free patients have been followed from one to eleven years with a median follow-up time of five years. The five years crude survival rate was 63%. Three patients died from cancer disease before five years, one after one year, one after two years and one after four years. More detailed results will be reported.

**Conclusions:** There is a need for a large-scale study of patients with verrucous cancers in the head and neck region in order to supply the best treatment modality. Such a study is best undertaken in a multicentre study due to small numbers with this histological type of cancer. Also uniform guidelines for the histological diagnosis need to be established. Proposals for such a study will be discussed.

**Adenocarcinoma of the ethmoid sinus. A review of 81 cases. Transfacial versus combined approach for anterior skull base resection.**

F Jegoux, C. Ferron, A. Faure, O. Malard, C. Beauvillain de Montreuil (Nantes, France)

**Methods:** We report on 81 adenocarcinoma of the ethmoid sinus. Post-operative morbidity, recurrences and survival rates of anterior skull base resection by transfacial approach and combined approach are compared.

**Results:** All cases were treated between 1988 and 2001: 5% T1, 10% T2, 35% T3, 29%, T4a and 21 % T4b (extension grading according ROUX). 34 patients were treated by transfacial approach without anterior skull base resection. Anterior skull base resections were performed by transfacial approach in 26 patients and by combined approach in 21 patients. Survival rate was based on Kaplan-Meier actuarial method. Survival rate was 85% at 1 year, 75% at 3 years et 60 % at 5 years. Local recurrences occurred in 3,5% and within 33 months on the average. Dura involvement and maxillary recurrence were associated with a poor prognosis. No survival rate difference were found between transfacial approach and combined approach. Overall complication rate were lower for transfacial than for combined approach.

**Conclusions:** In our experience, the transfacial approach for the anterior skull base resection improved the post-operative appearance and reduced the complication rate with similar survival rates and local control.

**The role of Iridium 192 afterloading combined with flap cover for the salvage of recurrent inoperable cervical metastases. A 20-year experience.**

P Rhys Evans, T. Upile, C. Nutting, K. Harrington, P. Kirkland, M. Henk, A. Searle, N. Horlock (London, United Kingdom)

**Background:** Recurrent cervical metastases that are considered microscopically irresectable in patients with head and neck cancer pose a formidable challenge. These patients have received radical radiotherapy and surgery, therefore therapeutic options become limited. Interstitial irradiation combined with surgical debulking may provide a modality for local control.

**Methods:** Since 1978 72 patients (age range 43-77 years) with recurrent irresectable neck malignancy (from oral cavity, pharynx, larynx or salivary gland) have been treated with surgical debulking and Ir 192 afterloading. All patients had had previous surgery, radiotherapy or both. An early group (Group 1) underwent debulking and afterloading. A later group (Group 2) underwent debulking, afterloading combined with flap cover to resurface the area. Complication rates, local control and overall survival were recorded and stored in departmental databases. Probability of relapse was calculated by the Kaplan-Meier method.

**Results:** There were 13 patients in group 1 and 59 patients in group 2. The Deltopectoral flap was the commonest flap used for resurfacing (50%) followed by the Pectoralis major and Latissimus Dorsi. In group 1, local complication rates were unacceptably high with over 20% resulting in major wound breakdown requiring additional flap cover. In group 2 there was only 1 major wound breakdown (2%) requiring further flap cover. Overall local control rates were approximately 60% at 2 years and 20% at 4 years. In field recurrence was 50% at 2 years while out of field recurrence was 60%

**Conclusions:** Afterloading combined with surgical debulking and flap resurfacing is an effective salvage modality in recurrent irresectable head and neck malignancy and can provide effective local control in some patients. Flap cover is an essential adjunct to this procedure to reduce complication rates to an acceptable level. It also may facilitate additional therapies after further recurrence.

**Postlaryngectomy pharyngocutaneous fistula and stenosis: incidence, predisposing factors and therapy**

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**Introduction:** Stenosis and pharyngocutaneous fistulas are frequent complications after pharyngolaryngectomy for extended (T3-T4) or recurrent squamous cell carcinoma (SCCA) but these events were scarcely reported.

**Aim:** To evaluate the incidence and the predictive factors of those complications since reconstructive surgery has been currently available.

**Methods:** From 1984 to 1997, 135 patients were consecutively treated for SCCA of the (pharyngo) larynx.

Primary surgical treatment was delivered with curative intent in 60 patients, 42 of the 60 patients after treatment with induction chemotherapy (with Cisplatin and 5 FU). 75 patients underwent surgical salvage following radiotherapy failure: for persistent tumor in 11 cases and for recurrent tumor in 64 cases. The nutritional score was calculated initially for each patient, using the WHO recommendations. We divided patients in two groups score according to a  $\leq 5$  score (poor-fair) and a  $> 5$  score (good).

**Results:** Stenosis was experienced by 7 patients (5.1 %): 5 patients in the group treated with planned surgery, 2 patients in the group of salvage surgery after radiation failure. All the patients had an initial reconstruction with a flap, four of the patients had also a pharyngocutaneous fistula. Three patients were treated with subsequent dilatation, 3 patients needed a second flap to solve the complications. All 7 patients needed a gastrostomy for nutritional support, three on a temporary basis, 4 patients has to conserve it definitively.

Pharyngocutaneous fistulas developed in 48,8 % of the patients (66/135); twenty-nine patients (48,3 %) in the group of patients treated by initial surgery and 37 (49,3 %) in the salvage surgery group. The mean time of apparition of a fistula was 9 days (range: 3 to 28 days) in the first group and 13,7 days in the second group (range 2 to 59 days). The mean time for closure was 27,2 days in the first group (range: 4 to 72 days) whereas it reached 47,8 days in the salvage group (range: 2 to 59 days). The fistula closed spontaneously within one month in 56 % of the patients: 20 patients in the first group, 15 patients in the salvage group. A surgical debridement was needed in 3 additional patients in the first group. Persistent fistulas required additional surgical flap repair for closure in 28 cases (39 %): 6 patients in the first group (10 %) and 22 patients in the salvage group (29 %). Univariate analysis showed that the site of the tumor ( $p= 0,001$ ), the nutritional score ( $p= 0,041$ ) and the salvage after radiotherapy ( $p= 0,0026$ ) were factors increasing the risk of the occurrence a fistula. A multivariate analysis, however, disclosed that the site of the primary tumor ( $p = 0,003$ ) and the necessity of a preoperative tracheotomy ( $p= 0,04$ ) were factors predictive of the occurrence of a fistula.

**Discussion:** The incidence of pharyngocutaneous fistulas after total (pharynge) laryngectomy is extremely variable with values ranging from 5 % to 65 %. There is not general agreement on the factors (related to the patient, the tumor, and the treatment) favoring the occurrence of pharyngocutaneous fistula.

Preoperative radiotherapy was found to be a significant factor in fistula formation. Weingard and Spiro found that, although previous radiation therapy was not associated with a higher incidence of fistula formation, the mean time to fistula closure was higher in irradiated patients ( $p < 0.05$ ). The extent of the tumor was also identified as significant factor predisposing the patient to the occurrence of fistula formation. This result support Medaelli de Zinis & al', results. In our study, a deficient nutritional status was significantly associated with the development of a fistula. Even though controversy still surrounds the occurrence of pharyngocutaneous fistulas, it's generally agreed that most fistulas respond well to a conservative treatment.

In our series, spontaneous closure was achieved in 69 % of patients who had not been previously irradiated versus 40,5 % of patients with previous radiotherapy. Stenosis was reported to be 48 % in the series of Kaplan (78 % for pyriform sinus cancer) and by

Mc Connel after primary closure, decreased to 10 % with free flap closure. In the series where this complications was not reported, it might well be more frequent, in particular when no immediate flap reconstruction were used. In our series, this complication was 5.1 %. The site of the primary tumor (hypopharyngeal v.s. laryngeal), the extend of pharyngeal resection and the use of immediate flap reconstruction are factors of importance as it is emphasized in the literature (Mc Connel & al., Weingard & Spiro).

Hypopharyngeal stenosis is a relatively frequent complication. Mc Connel & al. found that the most important determinate for it to occur was the site of the lesion (and the extend of the tumor). The best prevention of hypopharyngeal stenosis appears to be the invalide reconstruction when partial pharyngectomy needed.

**Conclusion:** Stenosis, a formerly frequent complication is becoming rare when appropriate reconstruction is applied: 5.1 % in our series. Fistulas are relatively frequent but the majority are resolved either with local irrigation or with subsequent flaps. In our series, spontaneous closure was achieved in 69 % patients who had not been previously irradiated versus 40,5 % of patients with previous radiotherapy. The site of the tumor was a significant risk factor for pharyngocutaneous fistula formation after an uni- and multivariate analysis.

#### **The clinical application of BMP7 for mandibular reconstruction**

M. Abu-Serriah, J. Barbanel, E. Odell, J. Devine, J. McMahon, A. Ayoub (Glasgow, United Kingdom)

**Background:** The aim of this presentation is to report on the preliminary clinical findings of using BMP 7 (rhOP-1) for mandibular reconstruction in humans.

**Methods:** The first phase of this investigation was conducted on adult sheep. A 35-mm mandibular osteoperiosteal continuity defect was created, and rhOP-1 with collagen carrier was applied in the defect. A mixture of woven and lamellar bone completely bridged the created defect in all the experimental animals; there was bone union between the regenerated bone and both proximal and distal bone.

**Results:** Based on the results of the experimental findings, the clinical phase of the investigation was conducted on four clinical cases; two cases with mandibular non-union and two cases for mandibular reconstruction following tumour ablation. In all the cases the bioengineered bone followed the same contour as the surrounding bone segments. No adverse effect was observed.

**Conclusions:** The clinical implications of these findings and further human application will be discussed.

#### **One-stage reconstruction of the supraglottic laryngopharynx after extended partial laryngopharyngectomy for T2 pyriform sinus cancer.**

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**Background:** despite advances in diagnosis and conservative surgery, total laryngopharyngectomy remains often the only suitable surgical approach for moderately advanced pyriform sinus cancer. The aim of this study was the assessment of an original technique for reconstruction of the supraglottic laryngopharynx.

**Methods:** between 1997 and 2002, 11 patients staged cT2 of the pyriform sinus underwent an extended partial laryngopharyngectomy. Four of them had previously external radiotherapy. The resection encompassed the upper two-third of the thyroid cartilage including the supraglottic larynx, the invaded pyriform sinus and the posterior pharyngeal wall. Reconstruction was achieved using a radial forearm free flap resurfacing the defect. The palmaris longus tendon harvested with the flap was tethered by securing it horizontally or vertically between the remaining muscles. Over-tension of the laryngeal portion of the flap was thereby achieved and airway collapse prevented.

**Results:** at 6 months, all evaluable patients (8/11) were able to speak and to breathe without tracheotomy tube. All by one were

able to eat normally, 1 patient remained feeding tube dependant. Two patients died in the postoperative period. Two patients died of distant metastasis at 2 months and 7 months. Another patient, continuously disease-free, died of another cause. With a follow-up ranged between 2 and 76 months (median: 20 months), 6 patients were alive and disease-free.

**Conclusions:** extended supraglottic laryngopharyngectomy is feasible for selected T2 pyriform sinus cancer, even when previously treated by radiotherapy. Use of the stretched radial forearm free flap provides an adequate one-stage reconstruction, optimizing functional outcome.

#### **Severe atherosclerosis of the radial artery in a free radial forearm flap precluding its use**

R. De Bree, JJ. Quak, JA. Kummer, S. Simsek, CR. Leemans (Amsterdam, The Netherlands)

**Background:** The free radial forearm flap is the most often used free flap for head and neck reconstructions. Survival of free flaps is dependent on adequate blood supply.

**Methods:** A 69-year old woman was scheduled for excision of a T3N0M0 oropharyngeal carcinoma, neck dissections and reconstruction with a free vascularized radial forearm flap. During the operation it appeared that the entire radial artery was almost completely obstructed by atherosclerotic plaques precluding microvascular anastomosis.

**Results:** Despite systemic risk factors certain artery types are more prone to develop clinically manifest atherosclerosis. There are no reports on the pathology of the radial artery in free flap reconstructions.

**Conclusions:** In head and neck cancer patients severe atherosclerosis of the radial artery is very rare, but if present makes free radial forearm flap reconstruction impossible. Therefore, only in patients with (risk factors for) peripheral vascular disease screening on radial artery stenosis must be considered.

#### **Macroporous Calcium-Phosphate ceramic associated with autologous bone marrow applied to bone reconstruction in irradiated territories.**

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**Background:** Radiation therapy and surgery produce irreversible effects on normal tissues, involving damages on their reparation properties. Calcium-phosphate ceramics are currently used in surgery as bone-bonding materials in normal tissues but have not been largely studied in irradiated areas.

**Aim:** The purpose of this study was to determine, *in vivo*, the bone behaviour and the bone ingrowths capacities in bone defects.

**Methods:** The study was performed after a localised and fractionated radiation therapy in a human-like model on dogs. Data were analysed at the expense of structured implants of micro macroporous Biphasic Calcium Phosphate (MBCP®, Biomatlante) filled by autologous bone marrow after implantation in irradiated soft and bone tissue. Histomorphometric examinations, qualitative scanning electronic microscopy and quantitative image analysis (quantimet © Leica) were achieved with variance analysis statistical assessment (ANOVA).

**Results:** Observations of implanted areas show that bone marrow graft injections increase the newly-formed bone amount, without any osteonecrosis. Bone formation is mainly present in close contact with ceramics inside the porous defects.

**Conclusions:** These results suggest that osseoconduction properties of ceramics remain important in irradiated bone. Bone marrow grafts can improve the bone ingrowths. This study provides the first results of BCP in irradiated areas in a human-like model.

### New micro-endoscopic applications in surgical oncology

T. Upile, P. Kirkland, S. Triaridis, P. Rhys Evans  
(London, United Kingdom)

**Background:** The micro-endoscope is a recent innovation that allows in situ magnification of up to 150 times. Our intention was to develop a workable protocol for the clinical use of the micro-endoscope and to develop this facility in a range of plastic and reconstructive surgery applications in the head and neck region.

**Methods:** Full ethical approval was granted. Initially ex-vivo specimens were used to refine the technique before collection of normative and pathological data from the examination of the upper aerodigestive tract in control and disease groups. Experiments were performed to determine sensitivities and specificities compared to histological standards. A range of clinical applications were explored, and photodocumented.

**Results:** A simple and reproducible protocol was developed for the clinical use of the scope. We present our experimental evidence suggesting sensitivities and specificities of over 90% in assessing normal and abnormal mucosa. A range of clinical applications were developed including the successful use of the scope in detecting metastatic squamous cell carcinoma deposits in the skin as well as for micro-vascular monitoring of free autologous jejunal flaps.

**Conclusions:** We have developed a workable protocol for the clinical use of the micro-endoscope and have developed the use of this novel facility in a range of plastic and reconstructive surgery applications in the head and neck region. We feel the micro-endoscope has great utility in mucosal monitoring, surgical margin analysis and micro-vascular free flap monitoring. The technique is simple, safe, efficacious, and repeatable with direct visualisation.

### Carotid management in head and neck tumors

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(Nancy, France)

**Background:** Head and neck tumors can involve carotid artery. Surgical treatment of these tumors is a difficult challenge. Our aim of our study, based on experience and literature, was to define the best preoperative and peroperative strategy.

**Methods:** Echography and MRI have to be performed if a carotidian involvement is suspected during physical examination. Preoperative evaluation of cerebral tolerance to carotid occlusion. Diagnostic angiography is performed to define the intracranial vascular anatomy, and to evaluate atherosclerotic disease.

**Results:** Elective carotid resection without reconstruction results in cerebral complications in 0 to 25% of patients, and death in 0 to 30% of patients. If a reconstruction by graft is performed, cerebral complications occur in 0 to 22% of patients, and in 0 to 33% of patients. However, many authors reported no stroke and no death after performing a preoperative permanent balloon occlusion of CIA associated with a carotid resection, in patients tolerating preoperative carotid occlusion test. In patients with advanced head and neck squamous cell carcinomas involving carotid artery, carotidian resection poorly improve the long-term survival, because of high postoperative cerebral complications rate. Preoperative carotid balloon occlusion predicts patients who can tolerate permanent occlusion. In patients non tolerating temporary occlusion, contralateral carotid endarterectomy must be discussed in cases of stenosis superior to 75%. Carotid resection is done secondary.

Carotid resection can be performed with an acceptable cerebral risk in selected patients. Preoperative carotid occlusion seems to result in decreasing of postoperative mortality and morbidity rates.