**Results:** The oxygenation of tumors decreased during the first cycle of RCTh and increased during the two-week break, followed by a maximum decrease of the pO2-value during the second course of RCTh ($p = 0.004$). The initially measured median pO2-value was a good parameter to predict tumor response to RCTh ($p < 0.01$). Follow-up of the first 10 patients who were measured from March 94 to February 95 suggest that a good oxygenation (mean pO2-value) after the two-week break correlates with a better prognosis ($p = 0.02$).

**Conclusion:** Preliminary results show that the initial oxygenation of the tumors as well as the reoxygenation during a fortnight break influence the tumor response to RCTh.

835 POSTER

## Randomized clinical trial of continuous accelerated irradiation (CAIR – 7 days a week) for head and neck cancer. Preliminary treatment results

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**Purpose:** Evaluation of preliminary (2-year) treatment results of 7 days a week continuous accelerated irradiation (CAIR) in compare to conventional radiotherapy

**Methods:** One hundred and one patients with squamous cell carcinoma of oral cavity, oro- and hypopharynx and supraglottic larynx in stage T2–4 N0–1 M0 were randomized between 2 groups: A (CAIR) – 52 pts and B (control) – 49 pts, and treated by radiation therapy alone in 1994–96. In majority (81%) there were the patients with advanced clinical stage (T3+T4). Irradiation technique and volumes, total and fraction doses were exactly the same in 2 groups of patients. Only the overall treatment time was shorter by about 2 weeks in CAIR group comparing to control because of the lack of weekend breaks.

**Results:** Ninety-eight patients (98%) completed the whole designed radiotherapy. Generally, 2-year local tumour control rate (LTCR) in CAIR arm was 85% and in control arm 40% ($p < 0.0001$). In aspect of tumour localization and stage the LTCR was significantly higher in CAIR arm than in control and was respectively as follows: 75% vs 26% in oral cavity, 86% vs 36% in oropharynx, 88% vs 50% in hypopharynx and supraglottis; 100% vs 64% for T2, 94% vs 39% for T3 and 66% vs 26% for T4. There were 14% of grade III and IV radiation morbidity in CAIR arm and 4% in control arm.

**Conclusion:** The high effectiveness of CAIR fractionation reflects the net effect of exclusion treatment weekend breaks and shortening the overall treatment time by 2 weeks.

836 POSTER

## Prognostic significance of irradiation of the posterior cervical lymph nodes in radiotherapy of oral cancer

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**Purpose:** We examined retrospectively if the inclusion of the posterior cervical lymph nodes (PCLN) in the planning target volume improves prognosis after radiotherapy of cancer of the oral cavity.

**Patients and Methods:** 188 patients were evaluated. 139 of them had been treated postoperatively (57 with inclusion of the PCLN, 82 without), 49 primarily (32 with PCLN, 17 without). These groups were evaluated separately. All patients were treated using lateral opposing portals in shrinking-field technique. Total dose to the primary varied mainly from 60–82.8 Gy (single dose 2 × 1.2 or 2.0 Gy), the dose to the PCLN varied from 30 to 60 Gy. Mean follow-up was 3.1 years.

**Results:** There was a bias between the groups towards a lower N-classification in patients whos PCLN had not been irradiated. Nevertheless, we never experienced a progression in the posterior cervical region during follow-up. In both groups locoregional tumor outcome, overall survival, progression-free survival and lymphoma-free survival were identical. Applying COX regression hazard model the dose to the PCLN never was an independent prognostic factor.

**Conclusion:** We think that radiotherapy of the PCLN can be omitted when there is no proven tumor involvement in the posterior neck triangle.

837 POSTER

## Inhibited expression of fibronectin in laryngeal squamous cell carcinoma cell lines

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**Purpose:** Molecular studies conducted on cell lines have demonstrated numerous alterations concerning the expression of different genes. A method called arbitrary primed PCR allows to detect changes in gene expression and does not require the construction of cDNA libraries. Aim of this study was to search for differences in the mRNA expression profiles of laryngeal squamous cell carcinoma (SCC) cells and normal keratinocytes from mucosa of the upper aerodigestive tract.

**Methods:** Total RNA was isolated from both cell types and reverse transcribed. cDNA was incubated with 0.2 $\mu$M of one of 26 decameric arbitrary primers, 0.2 $\mu$M of the corresponding anchored oligo (dT) primer, 2.5 $\mu$M dNTPs, 1.5 $\mu$M $MgCl_2$, 2 $\mu$Ci $^{33}$P-dATP, and 2.5 U Taq-polymerase in a final volume of 50 $\mu$l. PCR was then conducted as described previously. After electrophoresis transcripts of interest were recovered from the gel and cloned into plasmid vector for sequence analysis.

**Results:** Selective expression of a 191 bp mRNA fragment was detected in normal keratinocytes. Although the sequence represented only a part of the mRNA including 3' poly (A) end, database search revealed a 99.4% homology with human fibronectin gene.

**Conclusion:** Fibronectin plays an important role in cell attachment due to its high affinity to the cell surface. Inhibition of fibronectin expression on mRNA level may be one of the molecular mechanisms involved in carcinogenesis. The absence of this adhesion molecule on the surface of the tumor cells may give an explanation for the phenomenom of missing contact-inhibition which is characteristic for cancer cells.

838 POSTER

## Cyclin-D1-expression of oral squamous carcinoma in comparison to precancerous lesions and normal oral mucosa

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**Purpose:** Cyclin D1 (CD1) is one of the important molecules in G1 restriction point control of the cell cycle. In a number of tumors, and especially preneoplastic lesions, amplification of the related gene or increased protein expression have been found. The aim of the presented study was the quantification and assessment of distribution pattern of CD1 this tissues.

**Methods:** 127 biopsies from 70 patients were stained with a three-step immunoperoxidas protocol using the anti-CD1-clone DCS-6 (DAKO). Quantification was carried out with a true colour image analysis system (CBA-8000, Leitz), data were gathered in Excel 5.0 and consequently analysed with SPSS ($\alpha \leq 0.008$).

**Results:** Significant differences were found betweeen tumors grade 1 and grade 2 with high average values for CD1 in comparison to tumors grade 3 with mostly low or negative values for CD1. Further, no significant differences were found between normal lesions, leukoplakias and dysplastic lesions with mostly low values for CD1, and a distribution pattern of positive cells mostly confined to the suprabasal layer in the epithelium.

**Conclusion:** In oral squamous lesions CD1 seems not to be involved in tumor initiation as it has been shown for breast cancer. However, it may play role in tumor progression as is indicated by high values in well and moderately differentiated tumors. Whether the negative values in low differentiated tumors are related to a negative feed back after retinoblastom gene mutation will be pursued in our studies.

839 POSTER

## MIB-1 and ploidy in head & neck cancer (SCC H&N)

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**Purpose:** To determine whether the immunohistochemical expression of proliferation associated antigens (Ki-67/MIB-1) and DNA-aberration (DNA Index, ploidy) in addition to tumor volume are predictive for relapse-free-survival (RFS).

**Patients & Methods:** Between 1993 and 1994, 59 patients with advanced inoperable SCC H & N were allocated to radiation (RT) or RT with chemotherapy (RCT). 27 pts received accelerated RT. Primaries were located in the hypopharynx (26), oropharynx (15) and in the oral cavity (14). Fresh frozen specimens were used for Ki-67 labeling index (L.I.) and flow cytometry (FCM). Routinely processed parraffin embedded sections were stained using monoclonal antibody MIB-1. Feulgen staining was used for image cytometry (ICM). Prognostic impact on RFS was evaluated for T and N integer score (TANIS), different treatment modalities, age, grading, typing, MIB-1 L.I., Ki-67 L.I., ploidy, SPF and 5c-ER

**Results:** Median follow-up was 345 days (89–891 d). Survival and RFS were 39% and 31% at 2 years, respectively. In univariate analysis, MIB-1 (L.I. < Median: 57% RFS; L.I. ≥ Median: 11% RFS, p = 0.017); MIB-1 L.I. without accelerated patients (L.I. < Median: 57% RFS; *L.I.* ≥ Median 9% RFS; p = 0.006); ploidy (diploid: 38% RFS; peritriploid: 35% RFS; tetraploid: 10% RFS; p = 0.04); remission quality (CR @ 3 mos: 57% RFS vs. PR/NC @ 3 months: 0%, p < 0.001) and TANIS (TANIS 5: 48% RFS; TANIS 6: 36% RFS; TANIS 7: 0% RFS; p = 0.0341). In a multivariate Cox regression analysis including MIB-1, TANIS and ploidy, only MIB-1 was an independent prognostic factor (p = 0.0051).

**Conclusion:** After RT/RCT of SCC H & N remission @ 3 mos, TANIS and MIB-1 are prognostic factors.

840 POSTER

## Carboplatin as part of each fraction of treatment: Potential for improvement upon hyperfractionated irradiation in advanced head and neck cancer

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**Purpose:** To investigate if modulation with carboplatin shows potential for improvement upon the EORTC hyperfractionated irradiation trial in advanced head and neck cancer.

**Methods:** From february 1993 to January 1996 49 patients (3 Stage 3, 46 Stage 4) were treated with a regimen composed of 2 fractions a day. Each fraction consisted of 115 cGy preceded by 5 mg/m2 of carboplatin. Treatment was administered 5 days a week up to total doses of 350 mg/m2 of carboplatin + 8050 cGy in 7 weeks. There were 13 hypopharynx, 25 oropharynx, 4 oral cavity, 3 nasopharynx, 1 maxillary antrum and 3 cervical masses of unknown primary tumour. 39 patients presented with N+ (37% of N3, 63% of the nodes being fixed).

**Results:** 82% of patients tolerated treatment exactly as scheduled and 100% received the planned radiation dose. Local toxicity was similar to that reported in the EORTC trial. No renal, otic or neurotoxicity were observed. Hematological toxicity was moderate. 47/49 (96%) CR and 2/49 (4%) PR were achieved for an overall response rate of 100%. After mean follow-up of 30 months (12–45) the actuarial local control and disease-free survival are 73 and 59% respectively. The actuarial control of the nodes is 94%.

**Conclusions:** This schedule is very effective, shows potential for improvement upon the EORTC hyperfractionated trial, and merits investigation in multicentric clinical trials.

841 POSTER

## Carboplatin (CBDCA) + radiotherapy (RT) vs RT in inoperable stage III–IV head and neck (HN) carcinoma

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In attempt to improve results in pts with inoperable stage III–IV SCC-HN we administered CBDCA (45 mg/m2 d. 1–5 of the 1, 3, 5, 7 wk) concurrently with RT (70 G y/7 wk). From 11/92, 160 pts were enrolled; 156 are evaluable for response and toxicity. Pts were males (90%) and females (10%) with a median age of 52 yrs (45–71) and PS1 (0–2). Site: oral c. (30) orophar. (85), hypoph. (22), larynx (19). Stage: III = 22%; IV = 78%; 45% had N2–3. RT (76 pts) and RT + CBDCA (80 pts) group were well balanced according to PS, site, stage, Nstatus. 18/76 pts (23%) treated with RT achieved a CR vs 32/80 (40%) (p < 0.05). Median RT dose: 67 in RT; 66 in CBDCA + RT; CBDCA relative D.I. of 0.90. There was a prevalence of leukopenia in CBDCA pts; 3 yrs O.S. = 12.5% RT vs 35% (p < 0.01);

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## Prognostic significance of monoclonal antibody MIB-1 in early stage larynx carcinoma

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**Purpose:** To compare MIB-1 labeling index to clinical staging, histological grading and clinical outcome in early stage larynx carcinoma with regard to its prognostic value.

**Methods:** The tumor specimens obtained during primary surgical treatment of 21 patients with locoregional recurrences and of 26 recurrence free patients after endolaryngeal laser partial laryngectomy were examined for the detection of Ki67 antigen by standard immunohistochemical procedures with MIB-1 monoclonal antibody. Staining results were compared to clinical staging, histological grading and clinical outcome.

**Results:** MIB-1 staining occurred in 88% of the tumors. The percentage of positive nuclei varied between 8.5 and 35.4 (median 20.1; mean 22.02) for the recurrence group and between 2.6 and 29 3 (median 7.6; mean 9.95) for the control group. There was no significant correlation between expression of the antigen and tumor staging but between tumor grading and staining. Recurrent tumors had in average a more than double labelling index of MIB1 than non recurrent ones (p = 0.0001). Only 47.6% of patients with an above median labeling index were recurrence free after the first year compared to 87.7% in the below median group (p = 0.0005).

**Conclusion:** MIB-1 labeling index can provide useful prognostic information in early stage larynx carcinoma. Patients with a high MIB-1 labeling index seem to have a shorter recurrence free interval than patients with a low MIB-1 labeling index.

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## Phase II study of vinorelbine (NVB) in patients with metastatic and/or recurrent squamous cell carcinoma of the head and neck (SCCHN)

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**Aim:** To assess the efficacy and safety of NVB in patients (pts) with metastatic and/or locoregional recurrent SCCHN untreated by chemotherapy (CT) and with lesions outside previously irradiated fields.

**Methods:** The following eligibility criteria were required: histologically documented SCCHN; at least one bidimensionally measurable lesion, PS ≤ 2 (WHO), normal haematological, renal and hepatic functions, neo-adjuvant CT is allowed with 6 months wash out time, written informed consent. From March 1995 to December 1996, 28 pts were included; data are currently available on 21 pts. Main characteristics were: sex M/F 18/3, median age 54 (38–71), PS: 0 (0–2). The sites of primary tumour included oral cavity (2), oropharynx (9), hypopharynx (7), larynx (3), and the sites of metastases were: lung, liver, lymph nodes. Prior treatment: surgery (9), radiotherapy (18), neoadjuvant CT (3). **Treatment:** NVB was given at 30 mg/m$^2$ weekly until progression or unacceptable toxicity. If the absolute granulocyte count on day 8 was ≤1,000/$\mu$l or another toxicity of CALGB grade 3–4 occurred, the treatment was postponed for one week or until recovery.

**Results:** The overall response rate was 15% (CI: 3.2–37.9%): 3 partial responses in 20 evaluable pts. The duration of responses was: 20.16 and 18+ weeks. All responses were seen in lung metastases and in lymph nodes. The treatment was generally well tolerated, 22 of 152 administered cycles were delayed for haematological toxicity. Tolerance was analysed on all included pts, data are available on 21 pts. Neutropenia CALGB toxicity grade 3–4 was seen in 13 pts (54%). No severe mucositis, no nausea/vomiting and no case of severe neurotoxicity were recorded. The median number of treatment was 6 cycles and the median dose intensity 83.53% (56.7–100%).

**Conclusion:** Present data demonstrate a moderate activity and a good tolerance of NVB with our schedule for pts with metastatic and/or recurrent SCCHN.