

in oropharynx and hypopharynx. Second and third neoplasia are the main problem after 5 years of follow-up.

408

POSTER

#### ENRICHMENT OF TUMOR CELLS FOR CELL KINETIC ANALYSIS IN HUMAN TUMOR BIOPSIES USING CYTOKERATIN GATING

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The feasibility of using cytokeratin antibodies to distinguish normal and malignant cells in human tumor biopsies using flow cytometry was tested for increasing the accuracy of cell kinetic measurements. Four different antibodies were screened on a 48 tumors from two centres; 26 head and neck (Amsterdam) and 22 oesophagus (Leuven). First screening was done by immunohistochemistry (ICC) on frozen sections to test staining intensity and fraction of cytokeratin-positive (CK+) tumor cells. The antibody showing the most positive staining was then used for flow cytometry. Two broad spectrum antibodies (AE1/AE3, E3/C4) showed the best results with ICC (>90% tumors positive). Cell suspensions for flow cytometry could be made from frozen material by a mechanical method. Enzymatic methods failed for frozen material but were best for fresh material. Tumor cell enrichment was tested by gating on CK+ cells in flow cytometry using the best antibody. Average enrichment was 0.58 for head and neck tumors and 0.75 for oesophagus tumors; overall enrichment 0.65 (0 = no enrichment, 1 = pure tumor population). In several cases, 100% enrichment was achieved. We conclude that this method can significantly reduce errors in tumor cell kinetic measurements by reducing normal cell "contamination".

409

POSTER

#### NEOADJUVANT CHEMOTHERAPY (CT) IN LOCOREGIONALLY ADVANCED NASOPHARYNGEAL CARCINOMA (NPC). RESULTS OF A MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS

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The aim of this retrospective study is to determine prognostic factors for response to CT and survival, in patients (pts) treated with neoadjuvant CT and radiotherapy (RT) for locoregionally advanced non-metastatic NPC. From February 1988 to December 1992, 100 untreated pts received 3 courses of CT regimen with Cisplatin 100 mg/m<sup>2</sup> Day1 and Adriamycin 30 to 50 mg/m<sup>2</sup> Day1 for group I (36 pts), 50 to 75 mg/m<sup>2</sup> for group II (39 pts) and 75 to 90 mg/m<sup>2</sup> for group III (25 pts), repeated every 3 weeks, followed by locoregional RT. Response was assessed after 1 cycle of CT, before and after RT, by the measurement of node areas. Pts characteristics: 70% were men, median age 36.6 years (11-66 yrs); T1T2 = 26 pts, T3 = 25, T4 = 49, N2 = 39, N3 = 61; histology; UCNT = 64, non-UCNT = 36. All characteristics were well balanced in the 3 groups. The mean response rate after 1 cycle was 54.9%, after 3 cycles 78.8%. After RT, we observed 83% of CR, 14% PR and 3% of failure. Twenty seven pts relapsed. With a mean follow up of 27 month, the 3-yr overall survival (OS) was 73.5% and disease free survival (DFS) 64.2%. Age, sex, node area, histology, T, N, Adriamycin dose-intensity, clinical response to CT, duration of RT and delay between CT and RT were variables studied in univariate and multivariate analysis (Cox model). In univariate study, the factors influencing significantly OS and DFS were response after 3 cycles of CT ( $P < 0.05$ ) and response after RT ( $P < 0.02$ ), the age was significant only for DFS ( $P < 0.03$ ). The only variable influencing the response rate to CT was Adriamycin dose-intensity ( $P < 0.05$ ). In multivariate study, only the response rate to CT influence the survival ( $P < 0.02$ ).

**Conclusion:** High dose Adriamycin regimen seems to improve the response rate to CT, which is correlated to OS and DFS. Further studies with dose escalation of Adriamycin and growth factors should be done to increase the survival of the bad prognostic pts.

410

POSTER

#### TREATMENT OF UNRESECTABLE STAGE III-IV HEAD AND NECK (H/N) CARCINOMA USING SUPRADOSE INTRA-ARTERIAL TARGETED (SIT) CISPLATIN (P) AND CONCURRENT RADIATION THERAPY (RT)

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Sixty patients diagnosed with Stage III-IV H/N carcinoma between 6/93 and 9/94 were treated with SIT-P at 150 mg/m<sup>2</sup> weekly x4 using femoral access to angiographically placed microcatheter into the tumor vascular supply. Concurrent (day 1) daily RT was delivered to the primary tumor and overt nodal disease to 66-74 Gy at 1.8-2.0 Gy/fraction. Fifty-two (87%) of 60 patients completed the chemoradiation therapy protocol. Overall, for both primary/nodal disease, histological/clinical complete response was attained in 45 (79%), and incomplete response in 12 (21%) of 57/60 evaluable patients. The 1.5 year (median follow-up = 10 months, range 2.5-20) disease control above clavicle is 95% for 57 evaluable patients. Two deaths occurred during treatment. Grade III/IV toxicity has included gastrointestinal in 6, hematologic in 5, mucosal in 12 and neurological in 4 patients. Concurrent RT and SIT-P can be safely delivered with high response rates in unresectable Stage III/IV H/N carcinoma.

411

POSTER

#### CYTOMETRIC DNA ANALYSIS, FVIII-, MIB-1-, AND P53 ANALYSIS IN PREDICTING RESPONSE TO RADIOTHERAPY FOR T3 LARYNGEAL CANCER

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Image cytometry DNA analysis was performed in pretreatment biopsies of twentytwo T3 laryngeal squamous epithelial cancers. Patients were all submitted to full dose, 64 Gy, radiotherapy. Seven patients were cured while fifteen patients either recurred, displayed partial response or progressive disease during treatment. None of the cured patients harboured tumors with more than 20% 5cER (exceeding rate) while seven out of fifteen (47%) of the radiologically uncured group displayed 5cER over 20% ( $P < 0.05$ ). The results indicate that T3 laryngeal cancer with a high degree of DNA aberration display increased risk to require laryngectomy due to recurrence or persistent disease after radiotherapy. The results from FVIII-analysis, MIB-1-, and p53-analysis will also be presented.

412

POSTER

#### INSULIN RESISTANCE IN AMINO ACID TRANSPORT SYSTEM A IN HEAD AND NECK CANCER PATIENTS STUDIED BY POSITRON EMISSION TOMOGRAPHY (PET) AND CARBON-11-METHIONINE

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Cancer cachexia is a complex syndrome characterized by tissue depletion and insulin resistance. Head and neck region of seven healthy volunteers and four patients with squamous cell carcinoma were studied by PET and carbon-11-methionine during fast (P-ins  $8.1 \pm 4.7$  mU/l) and euglycemic insulin clamp technique (P-ins  $53.5 \pm 13.4$  mU/l). The transport rate for methionine was  $34.3 \pm 14.7$  and  $45.1 \pm 14.9$  umol/l/min for parotid gland of healthy volunteers (fast and clamp, resp.) ( $P = 0.0039$ ). In patients the transport rate for methionine was  $33.6 \pm 14.1$  and  $30.0 \pm 6.9$  umol/l/min in parotid gland ( $P = 0.51$ ) and  $49.3 \pm 12.3$  and  $45.8 \pm 10.5$  umol/l/min in tumor tissue ( $P = 0.37$ ). Amino acid transport system A is stimulated by insulin in parotid gland of control subjects while there is no response to insulin in parotid gland and tumor tissue of patients with head and neck cancer. Studies to increase insulin sensitivity in normal tissues of cancer patients to prevent cachectic metabolism are warranted.