

system before treatment (BT) and after 3 courses of CT. Objective response based on clinical examination (CE) and CT-Scan was achieved in 19/38 patients. The regression stage (RS) based on tumors histology obtained surgically ( $n = 28$ ) after 3 courses of chemotherapy was achieved in 8/28 patients. Total glutathione (GSH), glutathione-S-transferase (GST) activity and GST- $\pi$  content were assayed on cytosols of total blood. For each cycle and each pt, GST activity and GSH content were investigated by spectrophotometric assays, GST- $\pi$  by Western blot. According to CE and RS, our results showed difference between non responders (NR) and objective responders pt (R) only for GST activity. The difference was significant after one course of CT [according to CE for NR ( $5 \pm 2$  nmoles/min/mg) and R ( $4 \pm 2$  nmoles/min/mg) ( $P < 0.05$ ), according to RS for NR ( $5 \pm 2$  nmoles/min/mg) and R ( $3 \pm 1$  nmoles/min/mg) ( $P < 0.01$ )]. No difference were detected for GSH and for GST- $\pi$ . These preliminary results suggest that GST activity plays a role in the chemoresponse of HNSCC pts. Patients with decreased GST activity may be more chemosensitive than others. Indeed, it is too early to detect some correlation between disease free and overall survival.

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#### 403 POSTER TIME INTERVALS VERSUS PROGNOSIS IN COMBINED TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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The present study investigated whether clinical outcome correlated with the length of different time intervals associated with combined treatment of 186 cases of primary cancer of the oral cavity. Unexpectedly it was found that patients with short time to start of treatment had significantly worse prognosis than patients with longer time to treatment. Median survival was 27 months in the first group as compared to 77 months in the other. Further analysis revealed that in the group with short time to first treatment, significantly fewer patients received radiotherapy (RT), time intervals between surgery and RT was longer and the overall treatment time tended to be longer. From our study we conclude that a standardized combined treatment regime with careful planning of time intervals once the treatment has started, is more important to the outcome than variations in the duration of the time interval between first diagnosis and start of treatment. Patients with pre op RT had better prognosis than patients treated with post op RT. Chemotherapy did not have effect on patient survival.

#### 404 POSTER INTERSTITIAL BRACHYTHERAPY FOR ORAL CAVITY CARCINOMA: SEARCH OF THE FACTORS RESPONSIBLE FOR LATE COMPLICATIONS

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In order to identify the factors responsible for late postradiological necrosis (l.n.) a retrospective analysis of 100 pts with a squamous cell carcinoma of the oral cavity treated with Ir-192 interstitial brachytherapy (BRT) between 1967 and 1992 has been performed. M/F ratio was 73/27, median age was 57 yrs (range 21–82). There were 82 oral tongue, 9 floor of mouth and 9 cheek mucosa pts. TNM stage was: T1-13, T2-50, T3-37, N0-65, N1-31, N2-4. Pts received 60–75 Gy (m. 69.2). Linear activity of Ir-192 wires was 0.75–2.68 mCi/cm (m. 1.46). Dose rate (d.r.) range was 25–114 cGy/t (m. 57) and time of treatment was 53–280 hrs (m. 134). Overall 3-year survival was equal to 61%. At first clinical control, 2 mos after BRT, 95 pts obtained local CR. However, only 86 pts were disease-free (9 were N+). In the group of disease-free pts probability of 3-year disease-free interval was 55.8%. Severe (grade 2&3) soft tissue and bone l.n. occurred in 28 pts and 8 pts respectively. In 89% of cases l.n. was observed during the first 18 mos after BRT. Probability of 3-year l.n.-free interval was 71.5%. In the univariate analysis of the time to appearance of l.n. the following factors were considered: T-localization, age, sex, T-stage, total dose and d.r. Only the effect of the T-localization has been found to be statistically significant ( $P = 0.0004$ ).

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#### ADENOMATOUS GOITER AND THYROID GLAND CANCER

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Probability of cancer /Ca/ detection in the tissue of adenomatous goi-  
ter /A.g./ determines the way of treatment. 3591 patients with goiter  
have been operated in our department during 50 years (1945–1995). The  
share of A.g. has reached 68%. Of 595 patients with A.g. who have been  
treated over the last 20 years 178 (29.9%) presented with Ca in the tis-  
sue of recidives Ca was detected in 60% cases. The histological structure  
of our data: follicular Ca—45.7%, papillary Ca—19.7%, mixed form—  
30.8%, low differentiated—3.8%. We consider adenomatous and re-  
current goiter as a group of risk. The principles of a surgical operation:  
extrafascial resection of thyroid gland, obligatory revision of the regional  
lymphocollector, neck-dissection in the cases of metastatic damage of  
lymphatic knots. Patients with T3-4, N1, G3-4 receive gamma-therapy.  
We use no cytostatics. All patients after operation need thyroindinum or  
triiodothyroninum.*

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#### CARCINOMA OF THE NASAL CAVITY AND PARANASAL SINUSES: A RETROSPECTIVE STUDY OF 169 PATIENTS

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In the period 1963–1992, a total of 169 consecutive patients with carcinoma of the nasal cavity and paranasal sinuses were treated at our institution. The histological types included squamous cell carcinoma (75%), adenocarcinoma (22%), and undifferentiated carcinoma (3%). All adenocarcinomas were located in the nasal cavity and generally associated with occupational exposure to sawdust. Eleven percent of all patients had positive neck nodes at the time of diagnosis. A combined radiotherapeutic-surgical approach was used throughout the entire period. Twenty patients had no or only palliative treatment. The overall actuarial ten-year loco-regional tumor control was 37% and the corrected survival 36%. The failure pattern was 80% in T-position, 28% in N-position and 18% distant metastasis. Univariate analysis showed a significantly worse prognosis for high T-stage, nodal involvement, maxillary sinus tumors, low histological differentiation, and high age. In the Cox proportional hazards model, the strongest prognostic parameters were T-stage and differentiation. T-staging of maxillary sinus tumors according to Lederman (1970) was more prognostic than the AJC/UICC staging system. Finally, the present data revealed that the overall treatment results have not improved over the last three decades despite refinements in diagnostic and therapeutic capabilities.

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#### CURE RATE AFTER LONG-TERM FOLLOW-UP IN HEAD AND NECK CANCER

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Between 1973 and 1993, 1355 consecutive head & neck cancer patients were diagnosed and treated with a multidisciplinary approach, and followed until death or until 10 years with no event of disease. Primary patients incidence site were 615 in supraglottis; 280, oral cavity; 254, glottis; 126, hypopharynx; 33, oropharynx, and 47, nasopharynx. Local relapse rate was 20% and node-regional relapse rate other 15%. Distant metastases were observed in 6% of patients, mainly arising from nasopharynx (23%), followed by hypopharynx (11%). Main organ involved was lung (50%).

Median follow-up was 10 years (range 4 months to 15 years). Cancer cure was observed after 5 years in glottis, supraglottis, mouth and nasopharynx cancer and after 2  $\frac{1}{2}$  years in oropharynx and hypopharynx. Highest cure rate was 80% in glottis, followed by 70% in supraglottis, 45% in mouth, 30% in nasopharynx, 25% in oropharynx, and 20% in hypopharynx.

Second primary was observed in 7% and a third primary in 0.6% of the patients. Only in 7 patients the second or third primary was seen after 5 year of follow-up.

In head & neck cancer, curability is observed after 5 years from definitive therapy in glottis, supraglottis, mouth and nasopharynx, and earlier

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

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# **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".

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# **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.

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# **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  $\times 4$  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.

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# **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.

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# **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  $\mu$ mol/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  $\mu$ mol/l/min in parotid gland ( $P = 0.51$ ) and 49.3  $\pm$  12.3 and 45.8  $\pm$  10.5  $\mu$ mol/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.

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