also more frequent in the C alone arm: 5/21 versus 1/18. Other differences observed in favour of the C + AMI arm are: hypomagnesaemia > CTC-grade 1 in 2/18 versus 8/21. Side effects of AMI were short lasting hypotension in 7 pts and occasional sneezing. Other toxicities are until now not different between both treatment arms. A CR was observed in 2 and a PR in 21 pts (RR%: 60%). The study will continue to 60 evaluable pts. In case of significant reduction of toxicity by the addition of AMI further dose escalation of C is planned.

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## INDUCTION CHEMOTHERAPY BEFORE RADIOTHERAPY IN OROPHARYNGEAL CARCINOMA. A RANDOMIZED TRIAL

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From 2/86 till 3/91 at Institut Gustave-Roussy in Villejuif and at Oscar Lambret Cancer Center in Lille 166 patients with squamous cell carcinoma of oropharynx were enrolled in a randomized trial of two arms. Arm A (A): radiotherapy (RT) alone; arm B (B): chemotherapy (CT) followed by radiotherapy. *Inclusion criteria:* oropharyngeal tumor exclusively (posterior wall, glosso-tonsilar sulcus excluded), T2, T3, T4; N0, N1, N2a, N2b; M0. *Exclusion criteria:* palliation treatment, age >70, pretreated patients, second cancer. *Treatment plan* Arm (A): radiotherapy 70 grays in 7 weeks, 5 fractions a week on the tumor site and in both sides of the neck. Arm (B) 3 CT cycles d1–d21, with CDDP 100 mg/m$^2$ IVP d1, 5 FU 1000 mg/m$^2$ d1 to d5 in 24 h continuous infusion, followed 15 to 21 days later by the same radiotherapy protocol. *Results:* all the patients enrolled in the study were included in the analysis even 10 pts classified N2c, 1 posterior wall, 1 70 older, 2 pts with general contraindication to CT and 1 with two primaries. Out of 83 pts in (B) 79 received CT; 5 had a grade III leukopenia and 6 a grade II, 4 had a grade IV mucositis. CT was stopped before the 3$^{th}$ cycle in 12 pts for toxicity (5), progressive disease (3), refusal (4). Regression was evaluated by CT scan and clinical examination on primary and nodes; we observed 57% objective responses (RC 19%, PR 38%). The 2 groups of 83 pts were well balanced in age, T, N and histology. With a median follow up of 36 months, the results at 72 months show that 37 patients died in (B) versus (46) in (A) without statistical difference ($P$ = 0.12). Causes of death were: recurrences 28 VS 26, toxicity 2 VS 2, intercurrence 7 VS 1, second primary 8 VS 4, unknown 1 VS 4. Disease free analysis shows no difference and the 2 curves are similar, loco regional recurrence (LCR) 30 VS 21, LCR + MTS 0 VS 2, MTS 6 VS 6, second primary 6 VS 13.

*In conclusion:* chemotherapy with CDDP—5 FU does not improve the benefit of oropharyngeal carcinoma treatment comparatively to radiotherapy alone.

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## CYCLIN D1 GENE AMPLIFICATION IN HUMAN LARYNGEAL SQUAMOUS CELL CARCINOMAS: AN INDEPENDENT PROGNOSTIC FACTOR

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The gene dosage of cyclin D1 gene (CCND1) was examined in 51 primary laryngeal squamous cell carcinomas and amplification of the gene was found in 9 cases (17.6%). CCND1 amplification did not correlate with the clinico-pathological parameters. In a median follow-up period of 29 months the overall survival rate was 71.4% for patients affected with tumors displaying normal CCND1 dosage, and only 25% for patients with tumors carrying amplified CCND1. In multivariate analysis, only CCND1 and tumor size retained a statistically significant prognostic value ($P$ = 0.037, $P$ = 0.041). This is the first report in which CCND1 amplification is identified as a significant independent prognostic factor in laryngeal squamous cell carcinoma.

395 POSTER

## SURGICAL TREATMENT & FOLLOW-UP OF DIFFERENTIATED THYROID CANCERS: RESULTS FOR 290 PATIENTS

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*Aim of the study:* 1) Evaluation of the validity of the initial surgery with regard to the prognostic index (as defined by the E.O.R.T.C.)—2) Evaluation of the occurrence: of local recurrences (central compartment), of regional recurrences (lateral compartment) and of distant metastases—3) Impact of the former events on survival.

*Material and method:* 290 Patients (PTS) (110 M; 180 F) consecutively operated on from 1955 to 1994 in our Institution for differentiated thyroid cancer, placed on suppressive hormonal treatment with or without adjuvant $I_{131}$ treatment (mean follow-up 9.7 yrs; 0.5 to 38 yrs). Histology: 212 papillary CA., 31 well differentiated & 47 moderately differentiated follicular cancer respectively. 26 PTS had various surgeries before referral, definitive surgery assured = 119 total thyroidectomies (TT), 36 bilateral subtotal lobectomies, 39 total unilateral and subtotal contralateral lobectomies and 93 unilateral lobectomies. 3 PTS: isthmusectomy or tumorectomy. 7 PTS: tracheotomy was mandatory. Recurrent nerve chain node dissection: 77 PTS, lateral neck dissection: 75 PTS. $I_{131}$ was given to 140 PTS (10 for initial distant metastases, 32 for central node compartment invasion, 9 for locoregional subsequent recurrence, the remaining PTS for ablation of thyroid remnant). 34 PTS had additional external radiation.

*Results:* 235 PTS are alive, 55 PTS are dead (33 with recurrence). Among 208 PTS without either initial metastases or central compartment residual tumor after surgery, the Prognostic Index (PI) inferior to 50 (n = 94) predicts a 10 yrs Survival (S 10 yrs) of 99% versus 74% for 114 PTS with PI superior to 50 (p inf. to 0.0001). Among 6 deceased PTS in the PI inf. to 50 group, none died from CA (but one died with a recurrence). S 10 yrs of PTS with PI inf. to 50 with surgery less than TT (n = 62) is not different from S 10 yrs of same PI. PTS with TT (with or without $I_{131}$) (n = 21). Additional $I_{131}$ for PI sup. to 50 PTS (n = 54) ensure a S 10 yrs of 84% versus 67% for PTS (n = 60) who did not receive $I_{131}$ ($P$ = 0.14 Logrank).

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## REFLEX-OTALGIA: PROGNOSTIC RELEVANCE FOR RADICAL RADIOTHERAPY OF OROPHARYNX CARCINOMA

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In advanced diseases patients often claim reflex-otalgia (ReOt). Sometimes ReOt is the leading symptom, especially in the recurrence situation. Does this parameter have an impact on the probability of clinical CR under radical radiotherapy (RRT)? From Jan. 1991–Dec. 1994 36/76 pat (47%) treated with RRT for oropharynxca suffered from ReOt. 7/40 pat without and 8/36 with ReOt got simultan CDDP-therapy. The mean T-category for non-ReOt pat was 3.2, for ReOt pat 3.3. Also equal was the rate of N+ (72%). The mean age was 58 and 59 yr. 12.5% (non-ReOt) and 28 (ReOt) were female pat. The mean TD (Gy) was 72.1 (ICRU) for non-ReOt and 72.3 for ReOt pat. RRT was interrupted in 27% of non-ReOt (mean 11 d) and 31% of ReOt (mean 7.8 d) and stopped in 3 pat in either group. 75% (30/40) of the non-ReOt pat and 55.6% (20/36) of the ReOt pat ($P$ = 0.01) have reached a clinical CR. CT- and/or MR-imaging strengthened the clinical findings. Our results proof ReOt as a significant clinical parameter for radioresponsiveness and tumour control.

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## RISK FACTORS RELATED TO LOCOREGIONAL RECURRENCE IN SQUAMOUS CELL CARCINOMA OF THE SKIN

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A retrospective analysis was performed in order to identify the risk factors associated with development of locoregional recurrent disease in patients with primary squamous cell carcinoma of the skin. Step-wise logistic regression analysis was used which consisted of 1039 patients

treated from January 1980 to December 1989 at Ankara Oncology Hospital. Locoregional recurrence occurred in 187 (18%) of these patients within a mean disease-free period of 15 months. Age, sex, anatomical location, size of lesion, lymph node status at diagnosis, stage according to TNM classification, histopathologic differentiation, prior therapy, treatment modality, lesions arising from scar tissue (scar carcinoma), concomitant premalignant tumor of the skin, development of secondary non-melanotic skin carcinoma and second malignancy were used as variables which could be correlated with locoregional recurrent disease. No correlation was found between development of recurrence and prior treatment, second non melanoma skin cancer, second malignancy, premalignant skin tumor, sex or regional lymph node dissection. Although univariate analysis demonstrated that location, size, lymph node status, stage, histologic differentiation, scar carcinoma and treatment modality were associated with an increased risk of locoregional recurrence, it was found out that stage of the disease ($P < 0.001$), treatment modality ($P < 0.01$), tumor arising from scar tissue ($P < 0.01$) and histologic differentiation ($P < 0.05$) were statistically significant as risk factors of recurrence when a multivariate analysis was applied.

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## CHEMOTHERAPY (CT) WITH RADIOTHERAPY (RT): LARYNX PRESERVATION STRATEGY IN CERVICAL SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS (CSCCE)

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In order to evaluate a new strategy to increase long term survival avoiding laryngoesophagectomy (LE), from 5/1985 to 12/1993, 37 pts with CSCCE were treated with combined CT (CDDP 100 mg/sqm, day 1, FU 1000 mg/m$^2$q, day 1–4 in 96 h infusion) every 4 week for 4–5 courses and RT (split course in 27 pts: 30 Gy days 1–19, 20 Gy days 67–78; continuous in 10 pts: 60 Gy). LE was limited to pts with resectable residual disease at the end of the treatment program or local relapse after initial CR. Characteristics of pts were: median age 62 yrs, range 46–78, stage I: 4 pts, stage II: 13 pts, stage III: 20 pts (resectable 9/20). Response was documented in 33 of 34 evaluable pts (97%) with CR in 24 pts (71%). Three cases were not evaluable: fistula, toxic death and severe myelosuppression. As of January 1995, 13 pts are alive with a total 5 yrs survival of 32%. Relapses were observed in 21/34 responsive pts (local 14, distant 7). Salvage LE was performed in 6/14 local relapsed pts; 2 pts are alive at 41 and 15 mos.; two others progressed after 24 mos from LE; while the remaining pts deceased within 3 mos. All pts with stage I disease are alive and disease-free at 5 yrs, while no difference was detected between stage II (24%) and III (18%). Mortality due to toxicity of CT plus RT was 3% (1/37). In conclusion, combined CT plus RT provides at least the same expected long-term results as primary surgery but preserves the larynx in neatly one third of cases. Surgery could be advocated only in event of local relapse after failure of combined CT plus RT.

399 POSTER

## P53 SERUM ANTIBODIES IN HEAD AND NECK SCC

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*Purpose:* To determine whether a correlation existed between the presence of serum antibodies against p53 protein (SAAp53) and clinical and pathological features in a series of 80 consecutive patients with HNSCC. *Methods:* The presence of SAAp53 was studied by ELISA, and p53 gene expression in tumor samples by immunohistochemistry. *Results:* At diagnosis, 18.7% of the patients had SAAp53. Over-expression of the p53 protein was found in 54% of the tumor samples. All the patients with SAAp53 also exhibited overexpression of the p53 gene on the corresponding tumor sample ($P < 0.001$). In a univariate analysis, T stage ($P < 0.001$), nodal involvement ($P = 0.03$), the performance status (WHO $\geq 2$) ($P = 0.06$), and the presence of SAAp53 ($P < 0.0001$) were significantly associated with a decrease in disease-free and overall survival, when stratified on the type of treatment. In a multivariate analysis, only T stage ($P < 0.05$) and SAAp53 ($P < 0.001$) remained significantly associated with a decrease in disease-free and overall survival. The DFS rate at 2 years was 62% when no SAAp53 were detectable, compared to 12% when SAAp53 were detectable. *Conclusion:* SAAp53 was strongly associated with clinical outcome.

400 POSTER

## RADIOTHERAPY FOR PRIMARY CARCINOMA OF THE CERVICAL TRACHEA: A REPORT OF 30 CASES

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Primary carcinoma of the cervical trachea is a rare malignancy whose treatment is not clearly defined. This work describes the experience of three radiation oncology centers over 30 years.

Thirty patients (pts): 27 male, 3 female, median age 61 years, presenting with carcinoma of the cervical trachea (squamous cell in 27) have been treated by irradiation, as a definitive treatment in 26 pts, median dose 60 Gy (35–70 Gy), and postoperatively in 4 pts, median dose 58 Gy. The radiation response was assessable in 19 pts: 9 complete responses (2 for a dose lower than 60 Gy vs 7 for a dose of 60 Gy or more). The 5-year overall survival rate is 29% after definitive irradiation for a dose of 60 Gy or more compared to 0% for a lower dose, and 25% after postoperative irradiation. These results raise the question of further dose escalation, using endotracheal brachytherapy and/or conformal therapy, within prospective collaborative studies.

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## 5 FLUOROURACIL (FU) BLEOMYCIN (B), EPIRUBICIN (E), CISPLATIN (P) IN LOCALLY ADVANCED (LA), RECURRENT AND/OR METASTATIC (REC/MTS) UNDIFFERENTIATED CARCINOMA NASOPHARYNGEAL TYPE (UCNT) PRELIMINARY ACTIVITY/TOXICITY REPORT

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Based on accumulated efficacy and tolerance experiences (JCO 91, ASCO 91–92), in 01/92 we started a new Ph I–II study in LA and REC/MTS UCNT, combining four known active agents in UCNT. *Protocol:* FU 700 mg/m$^2$/d CIV d1-4, B 10 mg IV d1 + 12 mg/m$^2$/d CIV d1-4, E 70 mg/m$^2$/d d1, P 100 mg/m$^2$/d d5 (d1 = d21). As 3/95, 33 patients (pts) were enrolled, 23 M/10 F, mean age 50 years (15–71). PS (WHO): 0–1: 31, 2–3: 2, 16 pts with LA disease (T3–T4: 56%, N2–N3: 100%) (UICC-AJCC 87), 8 with isolated locoregional REC, 5 MTS alone and 4 bath. *Tumor sites:* 12 nasopharynx (NP), 6 bone, 3 liver, 2 extraregional nodes (ERN), 3 lung. All REC/MTS pts were pretreated, 6 RT alone, 11 pts CT + RT, 10 of them Platinum based. *Toxicity* (WHO): 111 cycles (c) and 33 pts evaluable, Gr3–4: mucositis 20c, in 7/8 pts preirradiated locoregionally, PNN 45c (22 pts), mean duration of neutropenia brief 3 days (1–7), Hemoglobin 9c (7 pts), platelets 15c (8 pts), febrile neutropenia 10c (7 pts), Gr3 nausea-vom: 5c (3 pts), Gr2 skin 4 pts, lung 3 pts, oto 2 pts, 1 death pulmonary fibrosis, 5-FU revesible cardiomyopathy 1 pt. *Response* (Res) (WHO) in LA disease (Group 1: G1) 16 pts evaluable after CT (1 CR, 14 PR, 1 NC) (ORR 94%) and 14 pts after RT (13 CR, 1 PD) (2 pts too early). In REC/MTS disease (G2) 16 evaluable (1 refusal), 4 CR and 8 PR, 3S D, 1 PD (ORR 75%). *Res by site:* CR liver 2/3, bane 1/6, ERN 2/2, lung 2/3, NP 4/12. In G2 median Res duration 10 m (CR = 6 + − 26+, PR = 5 + − 19). With median followup (FUp) of 16 m (4–39): G1: 11 NED (7 + − 25+), 2 AWD (13+, 22+), 1 DOD at 5 m and 2 still on treatment. G2: 4 still responding free of progression (12 + − 34+), 4 AWD (20 + − 34+). This regimen shows high CR in visceral sites, with good Res duration in the palliative setting and good activity as induction chemotherapy. A larger accrual is needed with increased FUp before comparing it with our current standard of B, E, P. (E. Cvitkovic *et al.*, ASCO 94.)

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## "GLUTATHION SYSTEM" AND CHEMORESPONSE TO 5-FLUOROURACIL AND CISPLATINE IN HEAD AND NECK SQUAMOUS CELL CARCINOMA: A PILOT STUDY

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The relationship between the glutathione system and the chemoresponse to neo-adjuvant chemotherapy (CT) commonly used (cisplatine/5-fluorouracil: CDDP/5-FU) in head and neck squamous carcinoma (HNSCC). We assayed in the total blood of 38 patients (pt) the glutathione