Afr. (including one total laryngectomy (TLE) for severe haemorrhage of a radiation ulcer). Mild laryngeal oedema was noticed in 35%, 22% and 38%., and persisting swallowing complaints were seen in 14%, 12%, and 9% for Cfr., HAfr., and Afr., resp. For patients receiving TLE for local recurrence, fistulae were seen in 14% (2/14), 29% (2/7), and 50% (3/6) after Cfr., HAfr., and Afr., resp.

Conclusion: In the Afr. schedule accelerated fr. started in week 3 and in the HAfr. schedule in week 4. This may account for the increased late toxicity in the Afr. schedule. Reducing treatment time by 2 weeks without reduction of total dose didn't result in increased toxicity using the HAfr. schedule.

368 POSTER

Interleukin-18 is constitutively expressed in head and neck squamous cancer cells

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Purpose: An imbalance of immunoregulatory factors is believed to contribute to immunosuppression associated with human head and neck squamous cell carcinomas (SCCHN). Interleukin (IL)-18 is a potent cytokine which promotes monocyte, macrophage and T helper 1 responses through induction of Interferon (IFN)-gamma by activated T cells. The aim of the present study was to define the production of IL-18 by SCCHN and its possible role in modulating the immune responses.

Methods: Expression of IL-18 in untreated and 5-fluorouracil (5-FU)-treated PCI4A and PCI13 SCCHN cell lines was analyzed by reverse transcription polymerase chain reaction (RT-PCR), flow cytometry, western blot and ELISA.

Results: We found that both PCI4A and PCI13 SCCHN cell lines express IL-18 at the mRNA as well as at the protein level. However, the protein is expressed intracellulary and predominantly released as unprocessed form (kDa 24). After exposure to 5-FU, an adjuvant therapeutic agent of choice for advanced SCCHN treatment, in both cell lines bioactive form of IL-18 was detected together with the inactive form.

Conclusions: The failure of SCCHN cells to process IL-18 raises the question of the role of the caspase 1/ICE in these cells. Experiments are now in progress to answer this question. However, these preliminary results suggest that 5-FU treatment promotes the processing of IL-18 in SCCHN cells, inducing the release of the active form of the cytokine that potentially can elicit an in vivo protective anti-tumor effects.

369 POSTER

Hemoglobin change, not hemoglobin concentration, has the predictive value in postoperative radiotherapy for locally advanced laryngeal cancer

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Purpose: Hemoglobin (Hb) concentration has an established prognostic value in radiotherapy alone for head and neck cancer. In our previous study, however, we could not confirm its value in a heterogeneous group of patients treated with postoperative radiotherapy (pRT) (Radiother. Oncol. Vol.56, Supl.1, p.158, abst. 598). The aim of this study was to investigate the predictive value of Hb concentration and Hb change in a subset of patients with advanced laryngeal cancer.

Material and Methods: Medical records of 690 patients with squamous laryngeal cancer treated with pRT in Centre of Oncology in Gliwice, Poland between 1980 and 1995 were reviewed for the analysis. The mean age of patients was 54 years. Male- female ratio was 9:1. There was considerable heterogeneity in total dose of pRT (20-72 Gy), fraction dose (1,5 - 2.5 Gy), overall treatment time, and Hb concentration (median-13,2). Median time from surgery to RT was 56 days. The data on locoregional tumour control were analysed using Cox proportional hazard regression model.

Results: A univariate analysis has shown that high Hb concentration at the end of pRT, and its increase during the course of irradiation were significantly related to longer recurrence-free survival, but Hb concentration after surgery was not significant. A multivariate analysis has shown that only change in Hb concentration during the course of irradiation appeared significant. A logistic analysis of a dose-response relationship suggest that a decrease in Hb concentration of 1 mg% could be compensated by an increase in radiation dose of 5 Gy, or by shortening of radiation treatment time by 8 days.

Conclusion: Hb change (but not Hb concentration) appears to be an important predictor of treatment outcome for patients with advanced laryngeal cancer treated with PRT. This shows a potential for treatment strategies aiming in increase and/or prevention of decrease in Hb concentration after surgery and during radiation treatment course.

370 POSTER

Parotid gland function following radiotherapy for head and neck cancer: dose/volume effects

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Purpose: To study the radiation tolerance of the parotid glands as a function of dose and volume irradiated.

Methods: 108 patients treated with radiotherapy for various malignancies in the head and neck region were prospectively evaluated. Lashley cups were used to collect stimulated parotid flow rate before, 6 weeks, 6 months and 1 year after radiotherapy. Parotid gland dose volume histograms were derived from CT based treatment planning. The normal tissue complication probability (NTCP) model proposed by Lyman was fit to the data. A complication was defined as stimulated parotid flow rate < 25% of the pre-radiotherapy flow rate.

Results: Size of the parotid gland, gender, age, tobacco and alcohol consumption, and tumour characteristics were not correlated with pre-radiotherapy parotid flow. A considerable variability in parotid output was found with a range of 0.03 to 1.66 ml/min (mean 0.34 ml/min). Reduction in post-radiotherapy flow rate correlated significantly with mean parotid dose. The NTCP model parameter TD50 (the dose to the whole organ leading to a complication probability of 50%) was found to be 31, 35 and 39 Gy at 6 weeks, 6 months and 1 year post-radiotherapy respectively. The volume dependency parameter n was around 1, which means that the mean parotid dose correlates best with the observed complications. There was no steep dose/response curve (m=0.45 at 1 year post-radiotherapy). No treshold dose was found.

Conclusions: A linear correlation between post-radiotherapy flow ratio and parotid gland dose and a strong volume dependency was shown. Recovery of parotid gland function was shown 6 months and 1 year after radiotherapy. Planning attempts should be made to achieve a mean parotid dose at least below 39 Gy.

371 POSTER

Treatment of advanced head and neck squamous cell carcinoma (HNSCC) with intratumoral cisplatin/epinephrine (CDDP/epi) injectable gel: Phase III multicenter studies

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Purpose: Therapeutic options for patients with advanced HNSCC are limited. We evaluated CDDP/epi gel for local tumor control and symptom relief in two identical Phase III placebo-controlled trials. This novel drug, designed for direct intratumoral administration, achieves high, sustained tumoral cisplatin concentrations with minimal systemic toxicity.

Methods: Adult patients with recurrent or refractory, histologically confirmed HNSCC were enrolled, stratified by tumor volume (up to 20 cubic cm), and randomized 2:1 to receive CDDP/epi gel (IntraDose Injectable Gel, Matrix Pharmaceutical, Inc.) or placebo gel. Maximum of 6 weekly intratumoral injections given in 8-wk period. Dose: 0.25 mL CDDP/epi gel per cubic cm tumor, up to 10 mL total. Patients with disease progression could crossover from the blinded to open-label study.

Results: 178 patients were evaluable. Most had been treated with multiple modalities: 89% of tumors were in a previously irradiated field. 119 patients (227 tumors) were treated with CDDP/epi gel; 59 patients (88 tumors) with placebo gel. Combined results from the two trials confirmed significant objective tumor responses (CR + PR) in these intensively pre-treated patients with poor prognoses: 29% (35/119), including 19% CR (23/119) for CDDP/epi gel, versus 2% (1/59) for placebo ($p < 0.001$). The response rate (CR + PR) for patients who previously had been treated with systemic cisplatin or carboplatin was 29% versus 30% for patients who were platinum naïve. Patients who crossed over from placebo to active drug treatment had a 27% (11/41) response rate. Tumor response and patient benefit were significantly associated (p=0.006): 47% of patients with

target tumor (the most symptomatic tumor) responses achieved a single, pre-selected primary treatment goal (e.g., improved wound care, better pain control) versus 15% of nonresponders. Pharmacokinetic studies showed peak plasma levels of total and free platinum 10- to 20-fold lower after intratumoral administration of CDDP/epi gel than reported for systemic cisplatin therapy. Patients treated with CDDP/epi gel experienced few of the side effects typically reported with intravenous cisplatin.

Conclusion: CDDP/epi injectable gel significantly reduces tumor burden, ameliorates tumor symptoms, and provides a new therapeutic option for managing patients with solid tumors such as HNSCC.

372 POSTER

Elective lymph node dissection following hyperfractionated accelerated radio-(chemo-)therapy for advanced head & neck cancer

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Purpose: The two years results of a German multicentre randomized trial showed that accelerated chemoradiation with MMC/5-FU to 70.6 Gy is more effective than accelerated radiation to 77.6 Gy alone at equivalent levels of acute and late radiation morbidity (abstracts ECCO10 and ASTRO 2000). Frequency, histopathology and impact on local tumour control of additive elective lymph node dissection were analysed.

Methods: Between 2/1996-8/2000 at T*bingen University 41 randomized patients plus 50 none-randomized patients with stage III/IV head&neck cancer were treated according to this protocol. Six to nine weeks after completion of accelerated (chemo)radiation an elective lymph node dissection was performed, if the primary tumour was in complete remission and clinical plus computed tomography proved residual lymph node disease. Nineteen of 39 patients with residual node disease underwent uni- or bilateral elective node dissection, the remaining patients had residual primary tumours, clinical detoriation or refused neck dissection. After elective node dissection one haematoma required additional surgical intervention and prolonged secondary wound healing was observed.

Results: After a median actuarial follow up of 24 months, 1 and 2 year overall survival was 81% and 64%, and loco-regional tumour control 64% and 56%, respectively. Three year loco-regional tumour control in randomized patients was 49% compared to 47% in non-randomized patients (log rank p=.78). Two-years loco-regional tumour control in stage cT4cN0 was 73% compared to 52% in cT2-4 cN1-3 tumours. Subgroup analysis of patients with involved nodes revealed a 2-year loco-regional tumour control in 58% (19/29 pat.) with complete remission of neck disease, 63% (12/16 pat.) with residual neck disease and elective node dissection versus 33% (12/23 pat.) without further treatment (p=.007). Restriction to patients with complete remission of the primary tumour revealed a 2-year loco-regional tumour control in 60% (16/22 pat.) with complete remission of neck disease, 75% (10/12 pat.) with residual neck disease and elective node dissection versus 33% (4/6 pat.) without further treatment (p=.08)

Histopathological examination showed viable tumour in 8 of 19 patients.

Conclusions: Elective node dissection of residual neck disease 6 to 9 weeks after completion of hyperfractionated accelerated radio-(chemo-)therapy contributed to loco-regional tumour control in advanced head&neck cancer.

373 POSTER

The hazard of ceiling effect for acceleration of postoperative radiotherapy of squamous cell head and neck cancer

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Purpose: To analyze the probability of loco-regional tumor control (TCP) in postoperative radiotherapy for squamous cell head and neck cancer (PRT) as a function of the average dose-intensity (DI) of radiation course.

Material/methods: The analysis included 942 patients in various locations and stages who were treated in Center of Oncology, Gliwice between 1980 and 1998. Mean total radiation dose, dose per fraction, overall radiation treatment time (OTT), and the interval surgery-radiotherapy were 62,4 Gy 2,1 Gy, 46 days and 62 days respectively. The heterogeneity in DI (mean 9.8 Gy/week, Std ±1.4) resulted both from unplanned treatment gaps and the diversity in dose/time prescription. Mathematical modeling of the relationship DI-TCP-dose has followed a statistical analysis of the clinical data.

Results: The data show that, for a given level of radiation dose, the relationship DI-TCP is non-linear, and increase in DI from 6 to 12 Gy/week results in steep increase in TCP, unlike increase in DI over 12 Gy/week, which brings only modest further improvement in local control. The same effect is predicted from theoretical modeling, which incorporates the effect of heterogeneity in radiosensitivity, repopulation, and subclinical tumor burden. For total radiation doses of 50 Gy or less such ceiling effect may appear at tumor cure levels below 80%.

Conclusion: The gain from shortening of OTT (and/or from increase in DI) is smaller than therapeutic lose from equivalent protraction of PRT. Clinical data on split-course therapy, or unplanned treatment gaps should not be used for prediction of gain from accelerated treatments.

374 POSTER

Recombinant human erythropoietin (r-HuEPO) corrects anemia and prevents transfusion during induction and concurrent chemotherapy during head and neck cancer (HNC) treatment

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The etiology of anemia in HNC is multifactorial, and can be caused by poor nutrition, low endogenous erythropoietin production, poor erythropoietin response, radiation and chemotherapeutic agents, and inflammation. We have previously reported preliminary toxicity and efficacy results of two sequential multi-institutional phase II taxane-based chemoradiation trials in locally-advanced HNC. This is a report describing the concurrent use of r-HuEPO in ameliorating treatment-induced anemia.

Eligibility: Previously untreated stage 3 or 4 squamous cell carcinoma of the larynx, hypopharynx, or base of tongue; no metastatic disease; good organ system function. Treatment: all 42 patients received induction chemotherapy with paclitaxel (P) 135 mg/m2 and carboplatin (CB) AUC 7.5 every 21d x 3 cycles. Patients with PR or CR at the primary site then received definitive RT (70-74 Gy in daily 2 Gy fxs) with concurrent P-based chemotherapy. Concomitant regimen 1 consisted of weekly P 30 mg/m2 q7d plus cisplatin 75 m2 d1, 22, and 43 (n=20). Regimen 2 consisted of weekly P 30 mg/m2 and weekly CB AUC 1 x 7 doses (n=22). All 42 patients were treated sequentially. Results: It was noted that 3 of the first 6 patients (50%) developed a moderate to severe anemia and required transfusions during chemoradiation to keep hemoglobin (Hgb) * 10 gm/dl. Thereafter, the treatment protocol was amended and all subsequent patients (n=36) received weekly r-HuEPO 40,000U in addition to induction and concurrent chemotherapy. Only 6 of 36 (15%) required transfusion after the addition of r-HuEPO. Median pre-treatment Hgb level in all 42 patients was 13.1 gm/dl, and was not different between groups. Without r-HuEPO, median end-treatment Hgb was 10.6 gm/dl. With the addition of weekly r-HuEPO end-treatment Hgb was 13.2 gm/dl, despite receiving fewer transfusions.

Conclusion: The use of weekly r-HuEPO 40,000U significantly reduced the need for transfusions and maintained hemoglobin throughout aggressive induction chemotherapy and concurrent chemoradiation in locally-advanced HNC patients. We are currently gathering long-term data to determine if maintaining a higher Hgb during treatment with r-HuEPO positively affects QOL and tumor control.

375 POSTER

Investigation of molecular targets for therapy in salivary glands carcinoma

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Purpose: Patients with recurrent and/or metastatic salivary glands carcinoma (SGC) respond poorly to chemotherapy. The availability of new selective drugs targeting receptors or molecular pathways warrants the conduct of studies assessing tumor-associated molecular alterations that will eventually drive new tailored therapeutic approaches in SGC.

Methods: Histologic types were: adenoid cystic carcinoma (ACC, n = 27), adenocarcinoma (ADC, n = 7), salivary duct carcinoma (SDC, n = 9), myoepithelial carcinoma (n = 5), mucoepidermoid carcinoma (n = 2), acinic cell carcinoma (n = 1) and undifferentiated salivary gland carcinoma (n = 1). The expression of estrogen (ER), progesterone (PgR), androgen (AR), and epidermal growth factor 1 (EGFR) and 2 (HER2) receptors was investigated by immune-histochemistry (IHC) on formalin-fixed archival