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

tissue in 38 cases. KIT expression by IHC was investigated in 24. In a different set of 14 cases in whom cryopreserved tumor specimen were available, co-expression of *c-kit* and its ligand (stem cell factor, SCF) was investigated by m-RNA RT-PCR analysis. Study of concordance between IHC and RT-PCR analysis for *c-kit* is ongoing.

Results: The results of IHC assessment in different histological types are:

	ACC	ADC	SDC	Other types	Total
c-kit	10/14 (71%)	2/4 (50%)	1/1 (100%)	2/5 (40%)	17/24 (62%)
HER2	1/20 (5%)	3/7 (43%)	1/2 (50%)	2/9 (22%)	7/38 (18%)
EGFR	7/20 (35%)	1/7 (14%)	1/2 (50%)	4/9 (44%)	13/38 (34%)
ER and PgR	0/20 (0%)	0/7 (0%)	0/2 (0%)	0/9 (0%)	0/38 (0%)
AR	0/18 (0%)	1/7 (14%)	2/2 (100%)	1/8 (12%)	4/35 (11%)

Of note, in this series of SGC a high proportion of cases (62%) expressed c-kit; while none expressed ER or PgR. Co-expression of *c-kit* and SCF m-RNA was shown in 2 of 7 ACC pts (28%), in 4 of 6 SDC pts (67%) and in one ADC patient.

Conclusion: A high proportion of SGC expresses c-kit and EGFR. Co-expression of *c-kit* and SCF, suggests a functional autocrine loop and was frequently detected in aggressive histological types such as SDC and ADC. The activity of new targeted drugs, such as hormone therapy, tyrosine-kinase inhibitors and monocional antibodies receptors aimed should be investigated in these rare tumors.

376 POSTER

Treatment of recurrent head and neck cancers: results of two radiochemotherapy (CT-RT) combinations

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The purpose of the study was to compare 2 different regimen of re-irradiation using the same CT-RT combination, but delivering 2 dimensionnal (2D) planning in one group (106pts) and 3 dimensionnal (3D) conformal radiotherapy (RT) in the other group (12pts).

118 patients with a history of prior irradiation (≥ 45Gy) were treated between 1988 and 1999 by RT combined with concomitant CT: Hydroxyurea (1,5g/d) and 5-FU (800mg/m2/d) from day 1 to day 5 for head and neck cancer. All patients were considered unresectable at the time of recurrence.The median age was 58 yrs (range, 28-78). The primary sites were oropharynx (43 pts), hypopharynx/larynx (35 pts), nasopharynx (16 pts),oral cavity (15 pts), combined sites (6 pts) and others (3 pts).The median dose prior to re-irradiation was 65 Gy (range, 45 to 80) and the median time to re-irradiation was 38 months (range, 4 to 288). RT consisted of 60 Gy in 12 weeks (10 Gy/week given by 2 Gy/fraction every two weeks) using 2-D treatment while the same total dose was given in 6 weeks when using 3-D conformal RT.

Results: Despite much more intense treatment in the 3-D group, the acute toxicity (mucositis, dermatitis, myelosuppression) was not significantly different between the two groups.A complete tumor regression was observed in 41% of the pts in the 2-D group and 58% in the 3-D group. However, given the short follow-up and the relatively limited number of pts in the 3-D group, conclusions regarding tumor response need further investigations.

Conclusion: The use of 3-D conformal RT allowed to increase the dose intensity of re-irradiation combined with chemotherapy, without increasing deleterious effect.

377 POSTER

Dosimetric evaluation of infield complications following chemo-radiation therapy for advanced head & neck cancers

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Purpose: to study the dosimetry in head & neck radiation treatments with and without intensity modulation (im) & correlate them with observed clinical outcomes on a prospective basis.

Materials & methods: 39 patients with locally advanced head & neck cancers were treated with concurrent chemo-radiation therapy (1.5 gy bid with taxol, 5fu & hydroxyurea; 5 days therapy followed by 9 days break; 4 to 5 such cycles). 18 patients had im (im group). 21 patients had radiation without dose im (nim group). Dosimetric evaluations (isodose curves & site specific maximum doses) were analysed. Acute & chronic toxicities were recorded using rtog criteria.

Results: there were no differences in the chemo-radiation doses (im=69.83gy, nim=70.14gy,p=0.93) at midplane central axis(cap). Maximum doses at cap was Nim=76: 25gy vs im=72.65gy,p=0.01. Maximum doses at the thinnest portion of the neck was nim=83.78gy vs im=73.55gy,p<0.001. Nim group patients had more treatment interruptions due to acute toxicities(43% vs 11%). After a median follow-up of 21 months, im group had lower gr 3 or 4 acute toxicities: dermatitis(50% vs 62%), mucositis(61% vs 90%), pain(28% vs 67%) and dysphagia(50% vs 67%). Im group had lower gr 3 or 4 chronic toxicities: skin(0% vs 24%), dysphagia(22% vs 43%), salivary gland(22% vs 38%). 4 patients of the nim group had postcricoid strictures, 1 had laryngeal stricture & 1 had mandibular radionecrosis. None of these occurred in the im group. These complications occurred at 'hot spots' on dosimetric analysis.

Conclusion: clinical toxicities observed in patients receiving radiation therapy with chemotherapy for advanced head & neck cancers are accentuated by dose inhomogeneities resulting from anatomic pecularities of the head & neck region. Techniques to reduce 'hot spots' should be considered in delivering high radiation doses to the head and neck region, especially when given concurrently with chemotherapy.

378 POSTER

Conformal boost radiotherapy for carcinomas of the naso-pharynx: local control and dose/volumes distribution

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Introduction: Conformal radiotherapy in cancers of the nasopharynx improves the dose distribution to the Planing target volume (PTV) compared to conventional radiotherapy. The aim of the study was to analyse the correlation between local control and dose-volumes distribution.

Material/methods: From 1995 to 2000, 17 patients (pts) with nasopharynx carcinoma had a boost conformal irradiation. There were 13 males and 4 females. The mean age was 47 years (18 to 69). There were 5 T2, 5 T3 and 7 T4 (4 N0, 1N1, 11 N2 and 1 N3) (UICC 1998). Six pts received a neoadjuvant chemotherapy (Bleomycin - Epirubicin - Cisplatin in 5 pts and 5 FU - Cisplatin in 1 pt) and 9 a concomitant chemoradiotherapy (Cisplatin x 3 and 2 cycles 5FU - Cisplatin). The first step of irradiation was a classical technique (2 or 3 fields treating the upper neck and the PTV and 1 anterior field treating the lower neck). The dose delivered was 50 Gy in 25 fractions. The boost to tumor PTV was applied by conformal radiotherapy with 2 to 5 fields. The energy used was X rays of 6 to 25 MV. The dose delivered ranged from 20 to 24 Gy (mean dose 21.3 Gy) in 10 to 12 fractions. The immobilization used was a thermoplastic facial mask. The technique of simulation for the last 9 pts was virtual (image acquisition with a helicoidal CT scan using a 3.2 mm slice thickness; drawing contours around the selected structures; multiple fields and customized focused blocks designed by Beam Eye View with a 5 mm margin around the PTV; isocenter treatment defined by virtual simulation placed under the accelerator; Digital Radiograph Reconstruction compared to the gammagraphy during the first session and calculation of the Dose Volume Histograms (DVH) performed for each volume).

Results: The mean follow-up was 20.8 months (7 - 53). Overall survival was 81% and 71% at 2 and 5 years. Local control was 88% at 9 months with a plateau. Mean PTV was 110 cc (27-253 cc). Mean minimal dose to the PTV (Dmin) was 59 Gy (33 - 71 Gy). Mean dose to 95% PTV (D95%) was 66 Gy (58 - 71 Gy). Mean PTV receiving minimun ICRU dose (prescribed dose - 5% = 66 Gy) (V66Gy) was 93% (58 - 100%). For local control, prognostic factors were: Dmin ~ 60 Gy (73% vs 0%; p = 0.04), D95% ~ 60 Gy (93% vs 0%; p = 0.001) and V66Gy - 90% (100% vs 0%; p = 0.00004) and - 95% (73% vs 0%; p = 0.04).

Conclusion; A dose > 60 Gy delivered to 95% PTV and more than 90% of PTV covered by the isodose 66 Gy seem to reduce the risk of local recurrence.