entire neck to a dose of 45 to 50.4 Gy over 5 to 5 1/2 weeks time. The interstitial implant to original tumor volume with 2 to 3 cm margins were performed under general anesthesia 2-3 weeks after completion of external beam irradiation. An interstitial implant boost varied according to the stage of disease, 20 to 40 Gy at dose rate of 40 to 50 cGy per hour.

Results: Overall local tumor control was achieved in 90% of patients and overall neck control was achieved in 91% of patients. Five year disease-free survival (Kaplan-Meier) for stage II disease was 85%, for stage III disease 75% and for stage IV 56.25%. The overall disease-free survival as well as overall survival for the entire group at five years were 77% and 40%, respectively. RTOG grade III and IV late sequelae occurred in 7.8% and < 2% of patients, respectively. The majority of patients had excellent cosmetic and functional outcome.

Conclusion: The combined modality including limited dose of external beam irradiation followed by interstitial brachytherapy in the treatment of carcinoma of the oropharynx yields excellent long term disease control with acceptable treatment-related morbidity as well as preservation of cosmesis and functional integrity.

364 POSTER

Is there a prognostic influence of tumor oxygenation measured after radiotherapy in patients with SCCHN?

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Purpose: Recent experimental data in SCCHN (squamous cell carcinoma of the head and neck) in nude mice of A. Ressel et al. (IORBP, No.4; 2001) showed a good correlation between the posttherapeutical fraction of polarographically measured hypoxic values and tumor response. In our present study we retrospectively evaluated in 39 patients whether a comparable effect can be observed in the clinical situation.

Patients and methods: The oxygenation status was polarographically (Eppendorf histograph) determined 3 weeks after the onset of treatment (30 Gy) and after the end of treatment (70 Gy). Patients were treated with radiotherapy alone (5x2 Gy/week, 70 Gy, n=11) or with radiochemotherapy (5x2 Gy/week, 70 Gy, mitomycin C, 5-FU, n=28). At 70 Gy we could perform measurements in only 19 patients due to tumor shrinkage under therapy.

Results: In the univariate analysis neither the polarographic hypoxic fraction (HF<5mmHg, p = 0,6) nor the median pO2 (p = 0,8) after 30 Gy had any relevance for the overall survival of our patients. At 70 Gy also no influence of these two factors (HF<5mmHg: p = 0,4; median pO2: p = 0,4) on overall survival could be observed.

Conclusion: In contrast to the experimental findings of A. Ressel et al. we observed no influence on overall survival of the oxygenation status during and after treatment. Furthermore, Ressel et al. observed an increase of the pO2 during therapy. However, we previously described under clinical conditions a decrease of the pO2 after 30 and 70 Gy, respectively (Stadler et al. Radiother. Oncol. 1998). Therefore, we conclude that these experimental data do not reflect the clinical situation.

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CT-based target contouring of the primary site in a prospective head and neck cancer trial: significance for a resident training program

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Introduction: In meta-analyses of Head and Neck Cancer, concurrent chemoradiation and altered fractionation schemes have shown to improve locoregional control and survival at the cost of increased toxicity. 3-D CRT techniques are currently implemented in sparing of normal tissues. Radioprotectors, like Amifostine, may further increase the therapeutic ratio. However, of paramount importance for the outcome is the adequacy in delineation of the target. In Rotterdam we started a prospective clinical trial of concomitant chemoradiation, randomized for Amifostine prior to RT. Of all primary tumor sites, e.g. larynx (L), piriform sinus (PS), base of tongue (BOT), tonsillar fossa/soft palate (TF/SP), the target was delineated independently by a resident in training and two senior radiation-oncologists on CT.

Patients and Methods: A treatment protocol was designed and guidelines were given for the standardization of the CTV of the (elective) neck nodal regions. No strict guidelines were given for the delineation of the primary tumor site. Per primary tumor site 3 patients were analyzed. The CT-based (MRI-matched) delineation of the primary targets and neck nodal regions was performed by an experienced resident (MB); contours were checked and modified by the physician in charge (senior staffmember) before the start of the actual 3-D treatment planning process. For the purpose of this investigation, the initial set of contours (MB) was saved, checked and modified a second (PL) and a third (PN) time. The contouring by PL, PN, being senior H&N radiation-oncologists, was solely for comparison purposes, that is without consequence to the treatment per se. An analysis was performed regarding the 3 sets of contours (MB, PL, PN).

Results and Discussion: The common volumes of the primary target for MB, PL and PN were quite similar, with little variation per site: MB-PL 85%, MB-PN 87%, PL-PN 86%. However, it is uncertain whether the missed volume (MB-PL 13%, MB-PN 12%, PL-PN 14%) is of clinical relevance. This has to do with the poor resolution of CT/MRI in e.g. BOT and TF tumors, but also due to lack of standardization. The first problem might be very difficult to solve at this time and age. With regard to the second problem: for conformal therapy treatment it is mandatory to provide the clinician with rigid guidelines for the primary tumor site, based on CT and MRI.

366 POSTER

Molecular detection of tumor cells in pharyngo-esophageal brush from patients with head and neck squamous cell carcinoma

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Pharyngo-esophageal brush-capsule (Oesotest®) with cytological analysis is a simple noninvasive technique for early detection of metachronous and recurrent head and neck squamous cell carcinoma (HNSCC). Microsatellite instability (allele shift) at tetranucleotide repeat markers is a clonal marker of HNSCC. We tested whether this marker could increase the sensitivity of oesotest® for detection of rare tumor cells, compared to cytological analysis.

A series of 56 patients with untreated HNSCC had an oesotest® before initial treatment. All these patients had an oesophagoscopy during endoscopy and no additional esophageal tumor was found. Our hypothesis was that oesotest® could collect rare exfoliated cells of the primary HNSCC tumor. Microsatellite instability with marker UT5085 was observed in only 14 of 56 (25%) primary HNSCC. Cytological examination with Papanicolaou staining and molecular analysis were compared for these 15 patients.

Cytological analysis could detect tumor cells in 6 out of 14 (43%) patients. Microsatellite instability was observed in 11 out of 14 (78%) of the same sampling (p=0.03). All cytologic-positive samples were also positive with molecular analysis.

Though cytological examination remains the standard method, this study suggest that molecular analysis could greatly increase the sensitivity of oesotest®. This study also emphasizes the need of other molecular markers in HNSCC

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Late toxicity in three fractionation schedules for advanced laryngeal cancer

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Purpose: Accelerated radiotherapy may improve locoregional control in advanced laryngeal cancer, however, late toxicity may increase. We compared late toxicity between two accelerated and a conventional fractionation (fr.) schedules.

Methods: Primary radiotherapy was performed in 132 patients with advanced laryngeal cancer, follow-up is at least 6 months. Sixty patients (1981-1990) were treated with conventional fr. (Cfr: 50 Gy elective dose, 70 Gy tumour dose; 5 x 2 Gy weekly); 29 patients (1994-1997) were treated with combined hyperfractionation (week 1-3: 30 x 1.2 Gy) and accelerated fractionation (week 4-5: 20 x 1.7 Gy): HAfr. (elective dose 53 Gy, tumour dose 70 Gy in 5 weeks); 43 patients (from 1997) were treated with concomitant boost: Afr. (week 1-2: 10 x 2 Gy, week 3-5: 15 x 1.8 Gy elective field and 15 x 1.5 Gy boost field; 47 Gy elective dose, 69.5 Gy tumour dose in 5 weeks). Interval between fractions was at least 6 hours. Field sizes were comparable between the three groups.

Results: For patients with local control severe laryngeal oedema, requiring intervention, was seen in 6% for Cfr., 6% for HAfr., and 15% for

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.

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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