model. The dose lost with the prolongation of OTT (decrease of dose per fraction) was lambda/alpha = 0.36 Gy/day, during the gap the proliferation is equivalent to lambda/alpha + delta/alpha = 0.67 Gy.

Conclusion: The repopulation of tumour cells is faster during the gap than during the normal days of irradiation.

600 ORAL

Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in cancers of the head and neck region

W. Dobrowsky[1], J. Widder[1], J. Naudé[1]. [1]*Allgemeines Krankenhaus der Stadt Wein, Dept. Radiotheraphy and Radiobiology, Vienna, Austria*

Purpose: To evaluate the effect of a very accelerated fractionation regime with and without chemotherapy (Mitomycin C) an advanced head and neck cancers a randomised trial was initiated following approval be the Ethics Committee of the Univeristy of Vienna.

Patients and Methods: From 10/1990 to 12/1997 a total of 229 patients (193 male, 36 female, median age 56 years, range 31–75 years) with squamous cell cancer of the head and neck region were treated in a randomised study comparing conventional fractionation (CF, 70 Gy/35 Fractions/7 weeks) with a continuous hyperfractionated accelerated radiotherapy (V-CHART 55.3 Gy/17 consecutive days/33 fractions) and the same fractionation with additional Mitomycin C (MMC: 20 mg/sqm on day 5 = V-CHART + MMC). Patients were stratified for age, gender, stage and site of disease, and performance status. Most patient had large inoperable tumours (T3/T4 84%, N1-3 79%). The mean Karnofsky performance status was 90–100% in all three treatment groups. Sites of origin were: oral cavity 70, oropharynx 95, hypopharynx 39, larynx 25.

Results: Main toxicity from accelerated schedules was confluent mucositis (Grade 3–4 in 95%) requiring naso-gastral tube feeding and analgetics in majority of cases, and moderate haematological toxicity (Grade III–IV: 29%) in those receiving MMC. The administration of MMC did however not influence local toxicity. The duration of mucositis in the three treatment groups was not statistically different.

	CF	V-CHART	V-CHART + MMC
Local tumour control	31%	34%	48%
Survival	27%	28%	39%

Twenty-one patients have experienced distant metastases, 9 patients second primaries, respectively. Follow up was >48 months (median) and assessment performed by January 1999.

Conclusion: Following shortening the overall treatment time from 7 weeks to 17 days and a reduction in dose of 15 Gy the results from the radiation only treatments are comparable. The administration of MMC to our accelerated regimen improves results significantly with regard to local tumour control and to actuarial overall survival.

601 ORAL

Randomized trial evaluating the role of blood transfusion prior to radiotherapy in 414 patients with head and neck carcinoma. A multicenter study by the Danish Head and Neck Cancer Study Group (DAHANCA)

J. Overgaard[1], H. Sand Hansen, M. Overgaard, C. Grau, K. Jørgensen, L. Bastholt, L. Specht. [1]*Danish Cancer Society, Dept. Experimental Clinical Oncology, Aarhus University Hospital, Denmark*

Background: As a part of a randomized trial evaluating role of nimorazole as a hypoxic cell radiosensitizer (Radiother. Oncol. 46: 135–46, 1998), the importance of hemoglobin (Hb) level on the outcome of radiotherapy and its modification with transfusion were also addressed.

Methods: Patients with low pre-irradiation Hb (females < 8 mmol/l, males < 9 mmol/l) were randomized to ± transfusion, prior to final randomization to nimorazole or placebo. Transfusion were given with packed red blood cells to achieve a Hb concentration in the "high" value range. If during the treatment the Hb level fell below the values indicated above, the transfusion was repeated. A total of 414 eligible patients with pharynx and supraglottic larynx carcinoma were included. High Hb was found in 243, and low in 171 pts. Among the latter 82 was randomized to receive transfusion (0–6 units). Compliance to tranfusion was high and all but six patients randomized received the treatment, but only in 29 patients were the required Hb level reached and matained during irradiation. Radiotherapy was conventional radiotherapy alone (62–68 Gy, 2 Gy per fx, 5 fx per week). Median obs. time was 112 months.

Results: Hb levels were not significantly related to any other major prognostic parameter (T-size, Nodal status, Tumorsite). Univariate analysis showed that the outcome (5-year actuarial loco-regional tumor control) was significantly related to Hb concentration (high 46% vs low 37%, p = 0.02), but transfusion to the low Hb group was unable to change the out come (39% vs 35% in transfused and non-transfused pts, respectively. Despite that, nimorazole did significantly enhance the outcome in all Hb strata, indicating the importance of tumor oxygenation and hypoxic cell radiosensitization. The lack of transfusion effect was unexpected, but may be explained by compensatory growth of tumor cells, since transfusion was given prior to start of radiotherapy. This may be avoided by a slow Hb increase during RT. Consequently this mechanism will be explored in a planned trial using EPO rather than transfusion.

Conclusion: Transfusion prior to radiotherapy was unable to improve the effect of radiotherapy of head and carcinomas in patients with low Hb values.

602 ORAL

A systematic review of chemotherapy trials in Head & Neck cancer

A.J. Munro[1]. [1]*R.O.D.S. Ninewells Hospital and Medical School, Radiation Oncology, Dundee, United Kingdom*

A literature-based meta-analysis of 73 randomised trials (11.355 patients) comparing standard treatment alone with standard treatment plus chemotherapy shows that adding chemotherapy improves survival by 8% (5% to 11%: NNT 10 to 20). The magnitude of improvement depends upon the timing of treatment: neoadjuvant 4% (ci 2% to 6%; NNT 16 to 50); synchronous chemo RT 16% (ci 11% to 21%; NNT 5 to 10). Loco-regional control is improved by synchronous chemo RT but not by neoadjuvant therapy: perhaps because the local procedure is compromised by a sense of false security. The modest survival benefit from neoadjuvant chemotherapy is due to a 7% (ci 4% to 11%) reduction in distant metastases. Synchronous chemo RT increases the rate of Grade 3 or 4 mucositis by 16% (ci 10 to 21%) – suggesting that there may be no real improvement in therapeutic ratio with this approach. These results imply that future trials need directly to address issues concerning morbidity and patients, attitudes to functional impairment.

Data from over 600 Phase 2 and Phase 3 studies of chemotherapy have also been systematically reviewed (15.353 patients). CR rate with platinum-based regimens is 32% (ci 31 to 33%); CR rate with regimens not containing platinum is 17% (ci 15 to 19%). CR rate is significantly higher in Phase 2 studies 36% (34 to 37%) than in Phase 3 studies 20% (19 to 22%). Early data, on 421 patients, suggests that Taxanes have significant activity in Head and Neck cancer: local disease CR rate 49% (ci 45 to 54%) for Taxane-based regimens. These data may be useful in putting the design of future trials in Head and Neck cancer on a more rational basis.

603 ORAL

Randomized study of fluconazole (FCA) oral suspension (OS) versus amphotericin b (ab) oral suspension in the treatment of oropharyngeal mucositis in head and neck cancer patients (HNCP)

C. Domenge[1], J.L. Lefebvre[2], Y. Esnault[3]. [1]*Gustave Roussy, chirurgie cervicio faciale, Villejuif;* [2]*Oscar Lambret, Chirurgie cervico faciale, Lille;* [3]*Laboratoire Pfizer, Orsay, France*

Mucositis is a frequent disabiliting side effect of anticancer chemotherapy and of radiotherapy. A randomized French multicentric study was conducted from March 1996 to June 1998 to compare the efficacy and safety of 2 regimen groups, FCA OS 50 mg o.d. vs AB OS 0.5 g q.i.d., for a period of 1 to 2 weeks in the treatment of mucositis in HNCP treated by radiotherapy and/or chemotherapy.

Methods: Inclusion criteria were HNCP with at least grade I mucositis during radiotherapy and/or chemotherapy, and who had direct swab examination and culture. Clinical symptom evaluation, direct swab examination and culture, were performed before treatment, at day 4 and day 7 and day 14 in case of clinical response.

Results: 268 patients (pts) were included in this study, 135 assigned to AB and 133 to FCA. The 2 groups were well balanced. There was no difference according to the gender (87% male), the age (28–90 average 58 ± 11), the weight (average 65 kg), anteriority of mucositis at inclusion (average 9 d ± 16). Mycologycal evaluation was positive before treatment in 46% of pts (C. albicans 65%, C. tropicalis 10%, C. kefir 9%, C. krusei 7%, C. glabrata 6%). Median treatment duration was 10.3 d (0–23) and 96%

of pts had a good compliance. The intention-to-treat analysis showed no difference for clinical global efficacy, cure or improvement, (54% AB, 52% FCA). For the pts who had Candida at the inclusion there was a difference in the percentage of negative cultures at the end of the treatment (34% AB vs 46% FCA, $p < 0.05$). No pts had disseminated candidiasis but we did not detect any neutropenia before or during treatment. FCA was preferred by the pts according to easiness of use (37% AB vs 58% FCA, $p = 0.0007$) and the taste (46% AB vs 73% FCA, $p = 0.0001$). There was no difference in term of safety between the 2 groups. Adverse events related to study treatment were mostly moderate gastrointestinal disorders.

Conclusion: Half the mucositis induced by radiotherapy and/or chemotherapy in HNCP can be cured or improved with antifungal therapy. FCA oral suspension 50 mg is as efficacious and safe as AB oral suspension 0.5 g q.i.d.

604 POSTER DISCUSSION 1

Clinical results of docetaxel (D) and 5 fluorouracile (5FU) in metastatic/recurrent squamous cell carcinoma of the head and neck (SCCHN)

N. Tubiana-Mathieu[1], D. Cupissol[2], G. Calais[3], P. Bontemps[4], H. Bourgeois[5], J.P. Dutin[6], M.H. Filippi[7], E. Saliba[8], S. Assadourian[8]. *[1]CHU Limoges; [2]Centre Val d'Aurelle, Montpellier; [3]CHU Tours; [4]CHU Besançon; [5]CHU Poitiers; [6]Centre St-Michel, La Rochelle; [7]Centre des Forcilles, Ferolles Attily; [8]Laboratoires Rhône-Poulenc Rorer, Montrouge, France*

D is an active drug in recurrent/metastatic SCCHN (response rates: 22 to 45%). D and 5FU were associated in a phase II study in patients (pts) with SCCHN. Pts received D 75 mg/m^2 1 h infusion followed by continuous 5FU 1000 mg/m^2 during 5 days, every 3 weeks (6 cycles, more in case of OR). After the inclusion of 20 pts, dose of 5FU was reduced to 750 mg/m^2 due to febrile neutropenia and mucositis. 63 pts have been treated. 54 were evaluable for toxicity and 44 for response. Of the 54 pts: 51 males/3 females; median age 53 years [40–70]; PS 0 (31 pts); 1 (23 pts); 75% of pts had locoregional disease, 21% had metastatic disease and 4 had both; 30% had previously received neoadjuvant chemotherapy (100% platin-based) and 95% prior radiotherapy. 212 cycles have been administered (median 3 [1.10]). Main toxicities (grade 3/4) were (per pt): neutropenia 65%; mucositis 30%; alopecia 11%; asthenia 11%; diarrhea 9%; anemia 7%; vomiting 2% and edema 2%. Febrile neutropenia occurred in 10% of Cy and 26% of pts. We had 4 toxic deaths among 63 patients: 2 of them were pts treated at 1000 mg/m^2 5FU dose-level. Overall response rate was 34% including: 4CR, 11PR, 15 NC, and 8 PD. Combination of D and 5FU is active in recurrent or metastatic head and neck cancer. Further evaluation of this association should be conducted in phase III trials.

605 POSTER DISCUSSION 1

Prognostic value of paranasopharyngeal extension of nasopharyngeal carcinoma (NPC)

E. Ciuleanu, T.E. Ciuleanu, V. Popita, N. Todor, A. Fodor, N. Ghilezan. *Oncological Institute Ion Chiricuta, Cluj, Romania*

Purpose: To assess the correlation between paranasopharyngeal extension and T category and to evaluate the prognostic value of paranasopharyngeal space (PPS) extension in local control and distant metastasis in pts with NPC.

Methods: Between 1995–98, 142 NPC pts entered the study. TN categories were defined according to Ho's staging system. Tumor extension into the PPS was defined as: grade (G) 0 – no extension, 1 – extension to the retrostyloid space, 2 – extension to the prestyloid space and 3 – extension to the anterior part of the masticator space. Relapse free, local relapse free, and distant metastasis free survival (S) were estimated using Kaplan-Meier method.

Results: 107 (75%) were men, age 48 [15–77], histology (WHO): I vs II vs III: 11 vs 40 vs 91 pts. The G 0, 1, 2 and 3 extension were 35%, 28%, 23% and 18% respectively. Extensive involvement of PPS (G2/3) appears in 45% of T2 tumors vs 63% for T3 tumors ($p < 0.05$). The 2-year relapse free S rate for G0/1 vs G2/3 extension was 67% vs 35%.($p < 0.01$.). The 2-year overall S for G0/1 vs G2/3 extension was 80% vs 54% ($p < 0.05$). The 2-year local control rate was 70% in G0/1 vs 46% in G2/3 ($p < 0.01$). When stratified for T classification (T2 vs T3), the difference was observed only in T3 disease. There was no difference in distant metastasis free S depending on the PPS extension (G0/1 vs G2/3: 91% vs 79%).

Conclusions: 1) Extensive paranasopharyngeal involvement (G2/3) was associated with poorer treatment outcome regarding relapse free survival rate, overall survival and local control rate. 2) Extensive involvement of the PPS correlates with advanced tumor (G2/3 more frequent in T3 vs T2 category).

606 POSTER DISCUSSION 1

Therapy of cervical lymph node metastases of unknown primary tumor

Antje Ernst-Stecken, G.G. Grabenbauer, R. Sauer. *Klinik für Strahlentherapie, University Erlangen-Nürnberg, Erlangen, Germany*

Purpose: Management of patients with cervical lymph node metastases of unknown primary site is discussed controversially. We address the outcome of radiation therapy (RT) as potentially curative treatment.

Methods: From 1981 through 1998, 78 patients with cervical lymph node metastases of unknown primary tumor received RT alone (n = 50) or simultaneous RT and chemotherapy (n = 28; 5-fluorouracil, cis-DDP) in curative intention. Fifty-five patients (71%) primarily underwent neck dissection. The treatment volume included the whole pharynx, both sides of the neck and the supraclavicular region. The mean radiation dose was 60 Gy (range 50–72 Gy), fifty-one (65%) patients received an additional boost radiation to the epipharynx with a mean dose of 10 Gy. Mean follow-up time was 7 years (median: 8 years).

Results: The cause-specific-survival rate (CSS) and locoregional control rate (LRC) for all patients were 51% and 76% at 5 years. The distant metastasis-free survival (DMF) was 68%. The addition of chemotherapy had no influence on CSS and LRC rate. Best results were achieved in patients treated after curative neck dissection (n = 47): CSS rate was 67% vs. 33% ($p = 0.006$), LRC rate was 94% vs. 52% ($p = 0.0001$). DMF survival was 83% vs. 50% ($p = 0.019$). CSS rate and LRC rate were also significantly better for patients who received more than 60 Gy ($n \approx 51$) to the epipharynx ($p = 0.03$).

Conclusion: The combination of surgery and RT in cervical lymph node metastases with unknown primary tumor is a safe and effective treatment. Prognostic factors of CSS and LRC were the extent of surgery (R_0 vs. $R_{1/2}$) and total dose (>60 Gy vs. ≤60 Gy).

607 POSTER DISCUSSION 1

Laterally pedicled V-Y advancement flaps for facial reconstruction

M. Ribeiro, L. Pontes, L. Santos, J. Videira, G. dos Santos. *Plastic Surgery Unit, Surgical Oncology Dep. I, Instituto Português de Oncologia, Porto, Portugal*

Introduction: Reconstruction of major defects in the face is generally achieved with pedicled or free musculocutaneous flaps, but, in less extensive defects, local flaps or gratis are ideal solutions.

Among the local flaps, we have a good experience with laterally pedicled V-Y advancement flap.

Methods: Between 1988 and 1998, 350 laterally pedicled V-Y advancement flaps were used for soft-tissue reconstruction in the face after oncologic resections. The advancement principle is based on the vascular flow to the flap via subcutaneous lateral bridges. In contrast to the regular V-Y flap, the central subdermal base is cut from top to bottom, so that the flap can be advanced more freely, only based on its lateral pedicles. This V-Y model was used in reconstructions all over the face. The lateral limbs of the "V" must lay on rest tension lines and plies of the face. This way, more extended reconstructions can be easily achieved, as wall as reconstructions in supra- and sub-orbital, pre-auricular, bucco-mandibular and periorbital zones

Results: In the 350 flaps that were performed using this principle, 3 complete necrosis occurred. All these 3 patients had previous local irradiation. In 10 flaps, there was local infection, resolved by conservative means. The flaps healed without further problems. Good cosmetic results were obtained.

Conclusion: In our experience, laterally pedicled V-Y advancement flap is the local flap more used and with better results in reconstruction of face defects.