Head and neck

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Management of cervical lymph node metastases from unknown primary tumours – Results from a Danish national survey

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The management of patients with cervical lymph node metastases from unknown primary tumours is a major challenge in oncology. This study presents data collected from all five oncology centres in Denmark. Of the 352 consecutive patients with squamous cell or undifferentiated tumours seen from 1975 to 1995, a total of 277 (79%) were treated with radical intent. The general treatment policy at all centres during the entire study period has been to treat all suitable candidates with radiotherapy to both sides of the neck and include elective irradiation of the mucosal sites in nasopharynx, oropharynx, hypopharynx and larynx (81%). Irradiation of the ipsilateral neck only was done in 26 patients (10%). Radical surgery alone, either lymph node excision or modified radical neck dissection was done in 23 N1–N2 patients (9%). The 5-year estimates of neck control, disease-free survival and overall survival for radically treated patients were 51%, 48% and 36%, respectively. The emergence of the occult pri-mary was observed in 66 patients (19%). About half of the emerging primaries were within the head and neck region with oropharynx, hypopharynx and oral cavity being the most common sites. Emerg-ing primaries outside the head and neck region were primarily located in the lung (19 patients) and oesophagus (5 patients). The frequency of emerging primary in the head and neck was significantly higher in patients not treated with radiotherapy compared to surgery alone, the actuarial risks at 5-year being 54±11% (no RT) vs. 15±3% (with RT), $p < 0.0001$. The most important factor for neck control was nodal stage (5-year estimates 69% (N1) 58% (N2) and 30% (N3)). Other important parameters for neck control and disease-specific survival included haemoglobin, gender and overall treatment time. Patients treated with ipsilateral radiotherapy had a relative risk of recurrence in the head and neck region of 1.9 compared to patients treated to both neck and mucosa. At five years, the estimated con-trol rates were 27% (ipsilateral) and 51% (bilateral; $p = 0.05$). The 5-year disease-free survival esti-mates were 28% and 45%, respectively ($p = 0.10$). In conclusion, this study has confirmed that patients with neck node metastases from occult head and neck cancer have clinical features and prognosis similar to other head and neck malignancies. Extensive irradiation to both sides of the neck and the mucosa in the entire pharyngeal axis and larynx resulted in significantly less loco-regional failures compared to patients treated with ipsilateral techniques, but only a trend towards better survival. A prospective randomised trial is required to determine the optimal strategy in terms of loco-regional control, survival and morbidity.

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18f-FDG PET is a sensitive tool for the detection of the occult primary cancer (CUP-syndrome) with head and neck lymph node manifestation

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Background: The neck lymph nodes are a common site of metastases from carcinomas of unknown primary (CUP syndrome). 2[18F]-fluoro-2-deoxy-D-glucose – Positron Emission Tomography (18-FDG-PET) has been shown to be a sensitive tool for detecting primary malignant lesions as well as metastatic spread. We have prospectively investigated the sensitivity of 18-FDG-PET in detecting occult primary carcinomas with manifestation in the head and neck lymph nodes.

Methods: From 5/94 until 7/98, in 723 patients a cancer of the head and neck was diagnosed at the Department of Otorhinolaryngology, Head and Neck Surgery of the University of Cologne. The routinely performed staging procedures were chest radiography, full blood count, cervical and liver ultrasound, endoscopy of the naso-, oro-, and hypopharynx, the larynx and the esophagus, and laboratory analyses. After the staging work-up, in 27/723 patients (3.7%) a CUP syndrome had to be presumed the primary cancer not being detected.

In these patients 18-FDG-PET was performed on a Siemens Ecat Exact 921 PET Scan with 370 MBq 18-FDG; images were reconstructed using a transmission – emission fusion technique.

Results: In 7/27 patients (26%) 18-FDG-PET revealed an unknown primary: in 2 patients a bronchial carcinoma, in 2 patients a nasopharyngeal carcinoma, in 1 patient a squamous cell carcinoma (SCC) of the parotid gland, in 1 patient a SCC of the hypopharynx and in one patient a carcinoma of the tonsil. In 4/7 patients the occult primary tumor was removed surgically. In a total of 8/27 patients therapeutic strategy was changed due to the 18-FDG-PET findings.

Conclusion: 18-FDG-PET should be performed in all patients suffering from a CUP syndrome after conventional diagnostic work-up fails to identify the primary.

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FDG-positron-emission-tomography as a diagnostic tool in radiation treatment planning of head and neck tumors

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Purpose: An individualized radiation treatment planning requires an exact definition of local tumor spread. Despite of high reliability of methods like CT, sono-graphy and MRI the correct diagnosis of lymphonodal tumor infiltration is often difficult. In a prospective trial, we examined whether an additional FDG-PET gives a relevant gain of information for radiation treatment planning.

Patients and Methods: We studied data of 34 patients with histologically confirmed squamous cell carcinoma of the head and neck who received a FDG-PET additionally to conventional staging procedures. The extent of changes of treatment strategy or target volume due to FDG-PET findings were analysed.

Results: In 41% of patients with primary tumors and in 58% of patients with recurrent disease FDG-PET detected additional tumor manifestations. In all cases changes of treatment strategy or target volume were necessary. Regarding patients with primary tumors the percentage of treatment modifications was highest in patients with large tumors (T3 and T4) (58%) and patients with advanced lymph node involvement (N2 and N3) (46%).

Conclusions: FDG-PET is able to give clinically relevant information compared to conventional staging procedures especially in patients with high risk of lymphonodal tumor spread. Therefore in patients with recurrent disease and patients with advanced tumor stages FDG-PET study prior to radiotherapy planning should be considered.

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Is repopulation of the tumour cells during radiotherapy doubled during treatment gaps?

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The aim of this work is to analyse the proliferation of tumour cells in treatment gap during the radiotherapy for head and neck cancer.

Materials and Methods: Clinical material is based on the records of 1350 patients treated by radiotherapy alone in Maria Sklodowska-Curie Memorial Institute in Gliwice during the period 1980–89. All patients had histologically confirmed SCC of larynx or pharynx. The mean gap duration was 9 days, only 10% of patients were treated without gaps. The dose per fraction was in range of 1.5 to 2.5 Gy.

Patient data were fitted directly to the mixed linear quadratic model using maximum-likelihood estimation. Tumour proliferation was assumed to be exp(lambda*OTT) and additionally exp(delta*gap_duration) for days with treatment gap. Tumour stage or tumour localisation were introduced to equation as categorical variables.

Results: TCP was significantly correlated with dose of radiation, tumour progression (according to TNM), overall treatment time, and gap duration. Laryngeal cancers had better prognosis than cancers of oro- and nasopharynx.

Our model was significantly improved when the duration of the gap was introduced even in the presence of overall treatment time already in the

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.

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

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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.

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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)

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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.

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A systematic review of chemotherapy trials in Head & Neck cancer

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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.

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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)

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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%