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Influence of severe anemia on tumor oxygenation in squamous cell carcinoma of the head & neck (SCCHN)

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Purpose: To investigate the relationship between polarographically measured tumor oxygenation and Hb concentration in patients with SCCHN.

Patients and Methods: 114 patients with histologically proven SCCHN underwent pretreatment pO_2 measurements with an Eppendorf-pO_2 histograph. Measurements in healthy sternocleidomastoid muscles were made in 59 patients. The patients were divided into three groups according to their Hb level – severe anemia (Hb < 11.0 g/dl), mild anemia (female: Hb 11.0–11.9 g/dl/male: Hb 11.0–12.9 g/dl) and normal Hb (f: ≥ 12 g/dl/m ≥ 13 g/dl).

Results: No significant difference in tumor oxygenation could be detected between mildly anemic patients and normemic patients. Both, the proportion of values ≤5 mmHg and the median pO_2 in the severely anemic group were significantly below that of each of the other two groups ($p < 0.005$). There was no significant difference between the three Hb groups in the normal muscles.

Conclusion: A low hemoglobin concentration is associated with an inadequate oxygenation of malignant tumors and thus for an increased radioresistence. Consequently, a pretreatment correction of the Hb level as well as the maintenance of a sufficient Hb level during therapy could be a meaningful way to improve the oxygenation status of tumors.

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CT-assisted brachytherapy (BT) planning for nasopharyngeal cancer (NPC)

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Purpose: We reported excellent local control rates in NPC using external beam radiotherapy (ERT) and BT delivering cumulative doses up to 95 Gy (JCO 1998; 16: 2213–22), with local relapse-free survival of all tumor stages being 86% at 3-yrs. Aims of the current study were a) to use CT-images to determine the geographic accuracy of the *Rotterdam* tumor tissue (TT)- and normal tissue (NT) dose reference points (Radiother. Oncol. 1997; 45: 95–8), and b) to compare these dose reference points with a CT-assisted optimized dose distribution.

Materials and Methods: In our institution NPC is treated with ERT to a dose of 60 Gy (T1, 2a) or 70 Gy (T2b-4), followed by BT. In 15 study patients CT-scans were obtained with the nasopharyngeal applicator in situ. The target volume and critical normal structures were contoured and the dose optimized to lowest dose on target, using a 3D treatment planning system (Plato-BPS v. 13.3). TT coverage and dose distribution to NT, using both dose prescription methods, were correlated with pre- and post-ERT tumor extension.

Results: Target coverage using the *Rotterdam* TT- and NT dose reference points was found to be adequate in tumors staged ≤T2a (n = 5). For tumors staged ≥T2b (n = 10) and/or showing extension beyond the confines of the nasopharynx proper after ERT to a dose of 70 Gy, CT-assisted optimized BT treatment planning improved target coverage substantially.

Conclusion: In view of its ease of application and the highly conformal dose distribution, BT is the modality of choice for boosting small NPC. To improve target coverage for tumors ≥T2b, CT-assisted treatment planning is mandatory.

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Phase I-II study with docetaxel (D), cisplatin (C) and 5-fluorouracil (5-FU) in patients (pts) with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN)

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The safety profile and activity of the combination of D, C and 5-FU was determined in 48 pts with locally advanced inoperable SCCHN. They were treated with D and C as a 1-hour infusion followed by a continuous infusion of 5-FU during 5 days every 3 weeks up to 4 cycles whereafter they were treated with locoregional radiotherapy (RT). Doses in level I were 75 mg/m^2 of D, 75 mg/m^2 of C and 750 mg/m^2/d of 5-FU and in level II the dose of C was escalated to 100 mg/m^2. Due to infectious complications in the first 18 pts, ciprofloxacine (cipro) was added from day 5 to day 15.

So far, 21 pts in level I and 14 in level II could be evaluated. At level I, 11 pts completed treatment and 9 pts at level II. 2 pts died due to infectious complications. Important side effects were neutropenia, infection, asthenia and renal toxicity, which were more pronounced in level II. Before introduction of cipro, 3 of 13 pts in level I and 2 of 6 pts in level II developed neutropenic fever leading to hospitalization. After adding cipro, 0 of 7 pts in level I and 0 of 6 pts in level II developed such complications. Response evaluation in 29 evaluable pts showed an overall response rate or 76%. All pts were treated with RT without unexpected toxicities.

Combination of D, C and 5-FU is highly active in pts with SCCHN. Cipro decreased infectious complications. Level I is the recommended regimen for phase III testing. An update of 25 patients treated in level I and 23 pts in level II will be available at the time of the meeting.

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Pretreatment hemoglobin (Hgb) is associated with response to neoadjuvant chemoradiation therapy (CRT) in patients with oral cavity and oropharynx cancers (OC&OP SCC)

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Objectives: Determine whether Hgb at the start of neoadjuvant CRT is associated with locoregional tumor control and overall survival of patients with T2–T4 oral cavity and oropharynx squamous cell carcinomas.

Methods: 116 patients were treated on a neoadjuvant CRT protocol in Vienna from 1990–1996 consisting of radiation therapy (50 Gy/33 days), mitomycin C (15 mg/m^2, Day 1) and 5-FU (750 mg/m^2/Day 1–5). Tumor resection and neck dissection were performed 4–5 weeks after CRT. Hgb was measured 1–3 days before neoadjuvant treatment.

Results: Hgb at the start of neoadjuvant treatment was <14.5 g/dL in 85 patients and >14.5 g/dL in 31 patients. The 2 groups did not differ significantly in T- or N-stage, age or sex distribution. Complete pathologic response to neoadjuvant treatment was achieved in 48% patients with Hgb > 14.5 g/dL and in 14% patients with Hgb < 14.5g/dL ($p < 0.001$). 3 year locoregional control (LC) was 90% in patients with Hgb > 14.5 g/dL and 71% in patients with Hgb < 14.5 g/dL ($p = 0.02$). 3 year overall survival (OS) was 84% in patients with Hgb > 14.5 g/dL and 64% in patients < 14.5g/dl ($p = 0.03$).

Conclusions: Pretreatment Hgb is associated with response to CRT, LC, and OS in patients with T2-T4 OC&OP SCC.

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Cell surface molecules in head and neck tumours

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Purpose: To screen various tumour markers in head and neck tumours.

Methods: To use immunocytochemical staining with monoclonal antibodies (Mab) for screening malignant and non-malignant tissue specimens from more than 100 of cases.

Results: The data confirmed that basal cells of normal buccal mucosa showed high levels of Class I, II, & EGFr expression. In OSCC a significant minority showed loss of class I antigens and this deficiency was more evident for the polymorphic antigens. Most OSCC cases showed overexpression of EGFr and >50% were positive for class II antigens. In all class II antigen positive cases there was a high degree of T cell infiltration.

Parallel studies in >45 ameloblastomas demonstrated that; a) loss of class I antigens was equal or higher than in OSCC, b) the expression of EGFr was detected only in a small number of cases, and c) in no case was high T cell infiltration or class II expression found.

Conclusion: These data clearly confirmed that at least two important signals were necessary for aggressive growth of the heterogenous malignant cells of OSCC or salivary malignancy as compared with the benign cell variants found in ameloblastoma. The malignancy appeared to have the capacity to escape the immune detection mechanisms whilst at the same time gaining self perpetuating potential (as demonstrated by overexpression of EGFr). In conclusion the data suggested that the screening of cell surface molecules by Mabs could assist clinical managements.

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Treatment outcome in patients (pts) with loco-regional relapse (LRR) of undifferentiated carcinoma of nasopharyngeal type (UCNT)

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Between 03/87 and 12/95, 51 pts were treated for LRR of UCNT at IGR. Pts characteristics: M 37/F 14, median age 51 years [21–72], nodal staging of initial disease (ID) (UICC 1987): N0 13%, N1 10%, N2a 13%, N2b 18%, N2c 23%, N3 23%, 100% M0. ID was treated by radiotherapy (RT) 16 pts, associated to cisplatin-epirubicin based chemotherapy (CT) 34 pts; median delay between LRR and ID: 22 months (mts) [7–120]; site of relapse: nasopharynx 21 pts, with nodal involvement 16 pts, nodal alone 14 pts. Treatment according to LRR stage included: RT alone (13 pts), CT alone (11 pts), RT + CT (27 pts) with the same epirubicin-cisplatin based CT. With a median follow-up of 39 mts [2–120], median survival is 30 mts and evolution marked by metastatic spread in 25% of pts at 2 years. There was 13 long term surviving pts (>36 mts). Site of relapse, delay between ID and LRR, and status of nodal ID did not influence prognosis. LRR of UCNT can be controlled by RTñCT with some success. Lack of control with metastatic involvement could explain the poor prognosis.

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Proliferation rate as a predictor on nasopharyngeal cancer radiation response

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Backgound: Irradiation is still the treatment of choice in NPC treatment. Up to now there is no accurate predictor on radiation response, since that the similar histo-morphological pattern, as a well known prognostic factor can revealed a wide range of treatment outcomes. Cellular tumor behaviour such as proliferation activity is proposed to influence the radiation response since that the G2 and M phases are the most radiosensitive cells.

Purpose: to find out the role of proliferation rate and other clinical factors in NPC as a predictor of radiation response.

Materials and Methods: Clinical stage and radiation response were collected from 116 patients. The proliferation rate from those patients were obtained flow-cytometrically (S-phase fraction). The radiation response were established clinically (nasopharyngoscop), CT scanning and pathologically.

Results: The range of the patients age is 15–70 year, and 70% of the patients consist of male. The SPF mean was 14.62 ± 10.18%, and 65% of our patients were T3 and T4, whereby the N2-3 group consist with 75% of them. Fourteen percents of the patients were Hsu type I, 48% were Hsu type II and the rest are belong to Hsu type III. There is a significant correlation between the proliferation value with the radiation response ($p = 0.001$). The complete and incomplete radiation response group of patients has the SPF mean value of 11.3% ± 9% and 18.5% ± 11.7% respectively ($P = 0.001$, OR = 1.07), with cut off level at the SPF 11%. There were 61% of cases with SPF < 11% revealed complete irradiation response versus 39% with partial response. On the other hand there were 32% of patients revealed complete radiation response versus 68% with artial response ($p = 0.01$, OR = 5.5). There is no correlation between the proliferation rate and the radiation response with the histology pattern of NPC. Multivariate analysis (SPF, histological pattern, tumor and nodal size) shown that only SPF has a role to influence the radiation response ($p = 0.02$).

Conclusions: SPF as one of the proliferation rate parameter can be used as a radiation response predictor of NPC. It is assumed that the patients with high proliferation rate should be irradiated with the inconventional irradiation scheme such as hyperfractionated irradiation, or combined with other modality that will en chanced the radiation effect, since that the proliferation is to fast for once a day irradiation scheme.

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Influence of haemoglobin on radiotherapy of head and neck cancers

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Purpose: The role of haemoglobin (Hb) level prior to radiotherapy was examined in 3 groups of patientswith head and neck cancers. The role of Hb with regard to response to therapy and survival was evaluated.

Patients and Methods: Patients with laryngeal cancer treated by conventionally fractionated radiotherapy (CF) from 1972–1990 (N = 327), patients with oral cavity or oropharyngeal cancers treated by preoperative radio (CF)-chemotherapy (MMC + 5-FU) from 1985–1989 (N = 96) and patients with CF vs. accelerated hyperfractionation (V-CHART) with or without chemotherapy (mitomycin C) treated in a randomised trial from 1990–1997 were evaluated with regard to treatment response and survival in relation to their initial Hb level.

Results: The results indicate that Hb level influences both response rates and survival in patients treated by conventional fractionation (Larynx $p = 0.02$, CF-arm (study) $p = 0.03$). Hb influences response rates after radio (CF)-chemotherapy ($p < 0.005$), but not survival. After V-CHART the role of Hb is almost statistically significant at $p = 0.07$ for response and significant for survival ($p = 0.016$). In the trial arm V-CHART + MMC the influence of Hb was neither seen for response ($p = 0.8$) nor for survival ($p = 0.7$).

Conclusion: The role of Hb plays an important role in response and survival of patients undergoing radiotherapy as single modality therapy and radio-chemotherapy when radiotherapy is given as conventionalfractionation. There is no influence of Hb when a very short fractionation schedule is applied together with MMC, a bioreductive drug with preferential toxicity in hypoxic tumour cells. This underlines the importance of tumour hypoxia as a major factor for tumour recurrence and the necessity to find ways to improve tumour oxygenation and development of regimens with chemotherapeutic drugs with specific toxicities.

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Poor prognosis was found in nasopharyngeal cancer patients with low glucose-6-phosphate-dehydrogenase

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Nasopharyngeal carcinoma (NPC) is a tumor of endemic distribution among well-defined ethnic groups, prevalent in several world regions. Southeastern China and Taiwan have the highest incidence (about 30 per 100,000 persons per year). Glucose-6-phosphate-dehydrogenase (G6PD) deficiency, a sex-linked disorder, is one of the most common enzymopathies in Taiwan. The major role of G6PD is to generate NADPH to protect cells from oxidative damage and to reduce the risk of certain degenerative disease, such as aging and cancer. With such a high coincidence of epidemic distribution of NPC and G6PD deficiency, as well as the house-keeping function of G6PD in cellular oxidative defense, we investigate the correlation of G6PD activity with NPC. The stage of NPC was classified by ACJJ (1997) criteria. G6PD levels were determined in 117 consequent NPC male patients. The mean G6PD level was 7.53 U/gHb (with standard deviation of 2.32 U/gHb), that was much lower than normal individuals (normal ranging 8–18 U/gHb). In addition, 19.5% of NPC patients has low G6PD activity (<6.4 U/gHg); 11.1% of NPC patients has very low G6PD activity (<5 U/gHb), which was higher frequency than population in Taiwan (~4%). The level of G6PD activity had no correlation with tumor stage or lymph node metastasis, but was significantly correlated with treatment failure (recurrence and/or distant metastasis) (30% vs 15.8% of treatment failure cases in G6PD level less