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Genetic and expression profiles of squamous cell carcinoma of the head and neck correlate with cisplatin sensitivity and resistance in cell lines and patients.

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Treatment strategies for squamous cell carcinoma of the head and neck (SCCHN) are still based on TNM-classification. However, it is clear that biological features of the tumors have an independent impact on the clinical behaviour of SCCHN. Biomarkers may serve as predictive markers for clinical response to specific therapies. The aim of the present study was to examine genetic changes and gene expression profiles that might correlate with sensitivity to cisplatin (MTT assay) in 10 UM-SCC head and neck cancer cell lines. Five cisplatin-sensitive and five cisplatin-resistant cell lines were studied by comparative genomic hybridization (CGH), Spectral karyotyping (SKY), and cDNA microarray analysis. The five cisplatin-resistant cell lines demonstrated significantly more genetic imbalances (regions of loss and amplification) and chromosomal abnormalities than the five cisplatin-sensitive cell lines by CGH and SKY, respectively. Supervised clustering identified appromixately 60 genes that clearly distinguish between the two groups of cell lines. Some of these genes are known to be involved in tumor progression, metastasis and drug resistance. By RT-PCR, we further confirmed the differential expressions of tissue inhibitor of metalloproteinase 2 (TIMP-2) and TIMP-3. Low expression of the oncogene c-met correlated with chemosensitivity (cDNA microarray). In a clinical material of 29 patients with SCCHN that received induction chemotherapy, low expression of c-met (immunohistochemistry), one of the gene from the distinguishing set was seen in flow cytometrically diploid tumors ($p<0.01$) and tended to correlate with better disease-specific survival. We conclude that cisplatin sensitivity and resistance are related to distinctive differences in genetic and expression profiles in individual SCCHN tumor cell lines. The genes we have identified may serve as potential targets for novel treatment strategies.

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Phase II continuous 7 days per week irradiation concomitantly with chemotherapy in advanced head and neck tumors treatment.

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Concomitant radiochemotherapy (CHRT) for locoregional advanced head and neck cancer (HNSCC) resulted in improved disease control and survival. DDP and vinorelbin are both active in HNSCC treatment likewise unconventional radiotherapy regimes. This is probably the first schedule that combined continuous, accelerated radiotherapy (7days per week) with chemotherapy.

Purpose: To assess the tolerance and efficacy of proposed schedule of concomitant CHRT for HNSCC.

Material and Methods: Eligible patients had previously untreated, histologically proven HNSCC of the T3-4, N2-3 stage. Forty one involved patients are males of 52 mean age in good general performance status. The primary disease sites are 19 oropharynx, 6 hypopharynx, 6 larynx, 4 linquae, 4 metastases from unknown primary site and 2 nasopharynx. Treatment consisted of DDP (100mg/m2 administered in 1,22,43,64 day), vinorelbin (30 mg/m2 in 1,8,22,29,43,50,64 day) continuously with accelerated (7 days a week) irradiation (started on 23 rd day) to the dose of 68 Gy in 40 fr. Due to toxicity of chemotherapy doses of DDP and vinorelbin were decreased to 70 and 20 respectively after first 23 patients.

Results: Results were studied among 40 patients. There was one death observed due to respiro-circulatory failure during treatment. Median follow-up was 20 months. Complete local and nodal regression was observed in 35 (87,5%) and 33 (82,5%) of patients respectively. Recidivation of the disease was observed in 2 patients (5%). Distant metastases were observed in 5 (15%) patients. There were 9 (22,5%) death due to disease. Treatment was well tolerated. The most frequent toxicity included anaemia (>2 in 8%), leucopenia (>2 in 25%) thrombocytopenia (>2 in 4%), acute mucosities acc. to Dische score was from the range of 11-22.

Conclusion: Proposed schedule is effective and well tolerated. Randomised study is however needed to confirm results.

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Stereotactic radiotherapy (SRT) plus external radiotherapy as radical treatment in nasopharyngeal carcinoma (NPC) with first local recurrence (LR), Queen Elizabeth hospital experience

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Background: First locally recurred NPC was treated with re-irradiation in our institution. We used lower dose of external re-irradiation plus SRT, aiming to decrease serious long-term complication.

Introduction: This is a retrospective review of patients treated with radical external RT plus SRT in NPC patients with first LR from January, 1998 to May, 2002. Results including local control (LC), overall survival (OS), failure free survival (FFS) and complications of treatment were analyzed in March, 2003.

Method and Materials: 37 patients, 26 males and 11 females had radical reirradiation. Median age was 52.5. Histology showed 30 undifferentiated, 6 poorly differentiated and 1 moderately differentiated carcinoma. All patients were assessed by CT scans. 36 patients had MRI assessment. rT stage by UICC (1997) was: 5 T1, 7 T2a, 12 T2b, 10 T3 and 3 T4. 24 patients were treated with conformal RT, 50Gy in 17, 54Gy in 4 and 60Gy in 3. 13 patients received conventional 3 fields RT, 54Gy in 10 and 56Gy in 3. Majority SRT schedules comprised of 12Gy in 2 to 3 weekly fractions or 10Gy in 2 weekly fractions at 50-90% isodose lines. Median time from local control after the first course of RT to diagnosis of first LR was 29.7 months (4.7 to 150.9 months). Two types of follow up (FU) time were used. FU1 from diagnosis of first LR had median 28.5 months (9.0 to 55.1 months). FU2 from date of diagnosis NPC had median 59.0 months (29.1 to 196.5 months).

Results: No local failure for rT1 and rT2a patients at time of analysis. 5 had local failure, 2 in rT2b, 2 in rT3 and 1 in rT4. 3 patients had neck failure; 1 was salvaged by radical neck dissection and brachytherapy. 7 patients died, 3 from distant metastasis, 4 from complications. Treatment related death included 1 sudden death with exposed C1, 1 with uncontrolled maxillary artery bleeding, 1 sudden death with temporal lobe necrosis (TLN) and 1 due to aspiration pneumonia. Possible explanations for complications were hypofractionation in first course RT and too high cumulative dose contributed from first treatment, external reirradiation and SRT. By FU1, actuarial LC rate, OS rate and FFS rate at 2 years were 88.7%, 89.5% and 77.1% respectively. By FU2, actuarial LC rate, OS rate and FFS rate at 5 years were 93.7%, 85.3% and 77.2% respectively. 4 patients had TLN 9-42 months after reirradiation. 1 patient needed tube feeding and died of aspiration. 11 patients had cranial nerve palsies. 7 patients had different degrees of hearing loss. 10 patients had hypopituitarism.

Conclusion: The results showed that lower dose of external RT plus SRT achieved good local control in first LR NPC patients. However, survival was still limited by complication and distant metastasis. Complications might be decreased by (1) conformal RT < 54Gy/27fr, (2) SRT dose < 12Gy in 2 weekly fractions at 70% rather than 50% isodose level and (3) careful limitation of total dose received by vital structures.

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Cisplatin-DNA adduct measurements in head and neck cancer patients treated by chemoradiotherapy

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Background: The optimal dose and route of administration for cisplatin-based chemoradiotherapy in patients with irresectable locally advanced stage IV head and neck cancer (H&N) of the pharynx or oral cavity is currently subject of investigation in a randomized phase III trial. This trial compares selective intra-arterial (i.a.) supradose cisplatin (150 mg/m2) (with systemic rescue by sodium-thiosulfate) and systemic intravenous (i.v.) cisplatin (100 mg/m2). Both arms are combined with standard fractionated radiotherapy (70 Gy/7 weeks). In a previous study in non-small cell lung cancer it was shown that cisplatin-DNA adducts were of predictive value for treatment outcome after chemoradiation. In a subgroup of patients entered in the current trial we studied levels of cisplatin-DNA adducts in primary tumor and normal tissue.

Material and methods: After written informed consent, we obtained buccal cells, white blood cells (WBC) and/or a tumor biopsy before and 23