Poster Session

Head and neck cancer and endocrine tumours

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Phase I study of cetuximab (C225)in combination with cisplatin or carboplatin and 5-fluorouracil (5-FU) in patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R&M SCCHN)

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The background of this study is to investigate the safety of cetuximab, a chimeric anti EGFR monoclonal antibody in combination with platinum and different doses of 5-FU in pts with R&M SCCHN. Main eligibility criteria: KPS * 70, no prior palliative chemotherapy (CT), adequate biological functions and at least one measurable lesion. Cetuximab was given at a fixed dose: starting 400mg/m* and weekly 250mg/m*. The patients were randomised to receive either cisplatin 100mg/m* or carboplatin AUC5. Only 5-FU dosage was escalated through three dose levels, 600, 800 and 1000 mg/m*, continuous daily infusion x 5 days. CT cycles were repeated every three weeks. DLT were assessed during the first two cycles. So far, 53 pts have been enrolled, 28 in the cisplatin group and 25 in the carboplatin group. Median age was 56 years (36-70), median KPS 80 (70-100).

Results: 12 pts (6 carboplatin / 6 cisplatin) have been treated in the first dose level (5-FU 600 mg/m*). NCI-CTC Grade 3/4 drug related toxicity: vomiting (3pts), febrile neutropenia (1pt) conjunctivitis (1 pt). 2 DTLs occurred in the cisplatin group: Febrile neutropenia and elevated ALAT. 16 pts (10 cisplatin / 6 carboplatin) have been treated in the second dose level (5-FU 800 mg/m*). Grade 3/4 drug related toxicity: drug fever (1 pt), diarrhoea + vomiting (1 pt), vomiting (1pt), fatigue (1pt), thrombosis on catheter (1pt). One DLT occurred in the cisplatin group: Asthenia G 3. 13 pts have been enrolled in the third dose level (5-FU 1000mg/m*) (6 cisplatin / 7 carboplatin). Grade 3/4 drug related toxicity Catheter infection (1pt), Fanconi like syndrome (1 pt). Two DLTs occurred in the cisplatin group: Myocardial infarction (1pt with prior history of cardiac disease) and mucositis + febrile neutropenia (1pt). One DLT has been reported in the carboplatin group: Mucositis G3. For confirmation of tolerability 12 additional pts (6 cisplatin, 6 carboplatin) have been included at this third dose level. So far 2 DLTs have been reported in the cisplatin group: Nausea + vomiting G3 (1pt), mucositis + febrile neutropenia (1pt) and 1 DLT in the carboplatin group: Neurotoxicity G3. This group is still under DLT evaluation. Preliminary results of efficacy are available for 30 patients: 13 PR, 11 SD, 6 PD. Cetuximab can be safely combined with therapeutic doses of Cis-/ carboplatin plus 5FU. Updated data will be presented.

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Neoadjuvant chemotherapy plus radiotherapy versus radiotherapy alone and the quality of radiation therapy in the treatment of locally advanced nasopharyngeal carcinomas

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Background: To assess, in a retrospective study, if there is a long term benefit of adding neoadjuvant chemotherapy (CT) to standard radiotherapy (RT) for the primary treatment of locoregionally advanced nasopharyngeal carcinoma (NPC) patients (pts), taking also into account the quality of the RT: optimal RT (ORT) or poor quality RT (PRT), in terms of a lower total dose or prolonged overall treatment time.

Material and methods: Between 1/1990-12/1995, 185 locoregionally advanced NPC pts, UICC stage III (8 pts) and IV (177 pts), with histological WHO type II (34 pts) or III (151 pts), entered the study. M/F ratio was 124/61, median age 46 [8-78]. Combined CT+RT consisted in 3 cycles of neoadjuvant BEC (Bleomycin, Epirubicin, Cisplatin) or EC (Epirubicin, Cisplatin) followed by standard RT (70 Gy/ 7wks), versus the same RT alone.

Results: 175 pts were evaluable for long term follow-up, 81 pts had CT+RT (21 PRT) and 94 RT alone (28 PRT). *Response rate* (RR) at the end of the primary treatment was similar for CT+RT vs RT (89% vs 85%, p=.46). RR in the CT+RT arm was not influenced by ORT vs PRT (92% vs 81%, p=.35) but was different in the RT arm (ORT vs PRT: 92% vs 68%, p<.01). *Survival* (S) was not significantly influenced by the addition of neoadjuvant CT vs RT alone (5y S: 53% vs 44%, p=.16). Five-years S in the CT+RT arm was not influenced by ORT vs PRT (52% vs 56%, p=.81), but radiation quality decisively influenced S in the RT arm (ORT vs PRT: 56% vs 14%, p<.01). *Disease-free survival (DFS)* was similar for CT+RT vs RT alone (5y DFS 44% vs 40%, p=.3). DFS in the CT+RT arm was not influenced by the radiation quality (ORT vs PRT (45% vs 42%, p=.74), unlike the DFS in the RT arm (ORT vs PRT: 50% vs 19%, p<.01)*Freedom from local relapse* (FLR) was not different among CT+RT vs RT (5y FLR 62% vs 56%, p=.98). FLR in the CT+RT arm was the same for ORT vs PRT (63% vs 59%, p=.98), but difference was significant in the RT alone arm (ORT vs PRT: 67% vs 30%, p<.01).

Conclusions: Neoadjuvant CT+RT and RT alone results were similar in terms of RR, 5yS, DFS, FLR. In the RT alone arm, a poor quality RT gave significantly worse results for all these endpoints. In the combined modality arm, neoadjuvant CT efficiently compensated for the poor quality RT.

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Experience of the AJCC/UICC 5th edition nasopharyngeal cancer TNM in a single radiotherapy practice outside Southeast Asia

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Background: The 5th edition NPC TNM in 1997, based on Southeast Asian data, was a landmark change in classification for nasopharyngeeal carcinoma (NPC). Although heterogeneous populations exist in North America and Europe, no validation of the 5th edition exists for non-asian patients using a large patient cohort and several reports identify that ethnicity is important in predicting treatment response. This study was conducted to compare the 4th (1992) and 5th (1997) edition TNM classifications and to evaluate the potential effects of ethnicity, histology and TNM in a single institution outside of Southeast Asia.

Material and methods: The records of all 520 NPC cases (358:asian, 162:caucasian) treated at our institution from 1985-2002 were reviewed. Radical radiotherapy alone was used in 383, and 113 received induction or concurrent chemotherapy; the remainder were treated palliatively and contributed to the more advanced stage grouping. Stage distributions for both the 4th and 5th edition were determined. Percentage Variance Explained (PVE), a measure of variance in outcome prediction by each stage grouping scheme, and Balance (evenness of case distribution by groups) were calculated.

Results: The stage distribution for the 4th edition was I:27(5%); II:306.5%; III:56(11%); IV:407(78%) and for the 5th edition I:52(10%); II:137(26%); III:163(31%); IV:168(32%). Stage stratified 5-year cause-specific survival probabilities (4th edition) were: I:91%; II:96%; III:72%; IV:70% and (5th edition): I:93%; II:81%; III:75%; IV:56%. The stage distributions in both TNM editions were similar for asian and caucasians with no multivariate statistical outcome differences according to ethnicity or histological subtype. PVE was 2.1% (overall), 2.45% (asians) and 1.3% (caucasians) for the 4th

edition compared to 7.5% (overall), 8.6% (asians), and 7.6% (caucasians) for the 5th edition. Balance was considerably better for 5th than the 4th edition across all subgroups.

Conclusions: These data strongly indicate that the 5th edition TNM performs better overall, and for both asian and caucasian groups compared to the 4th edition TNM in a single institution outside Southeast Asia. Race and histology did not add independent prediction of outcome by stage in this series.

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Radiotherapy for oropharyngeal cancer. Results from 1998 to 2001 with emphasis on the correlation between treatment technique and side effects

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Introduction: January 1999 we changed strategy in our treatment of small lateralized oropharyngeal and oral cancers (retromolar trigone, anterior faucial pillar and tonsil without involvement of the floor of the mouth, tongue muscle and soft palate) and unilateral lymph node involvement, from bilateral parallel opposed fields to one of oblique wedged unilateral fields, treating only the ipsilateral elective lymph nodes.

Methods: The investigated population consists of all patients referred to our department for treatment of oropharyngeal cancer between January 1st 1998 and December 31st 2001. After treatment the patients entered follow up and side effects was continuously registered according to normal DAHANCA procedure. In the investigated period we received 115 patients with oropharyngeal cancer. There were 81 (70%) males 34 (30%) females. One hundred and four (90%) was treated with curative intent. Radical treatment was planned on our dose planning system (Helax TMS). The standard regimen included a total radiation dose of 66-68 Gy to tumor planning target volume and 46-50 Gy to elective lymph nodes, 6 fractions per week, 2 Gy pr. fraction, and nimorazole. Patients were treated on a linear accelerator using 4-6 MV. Ipsilateral treatment consisted of 2 wedged fields was given to 31 patients. Bilateral treatment (73 patients) consisted of two opposing beams for the large fields and opposing orthogonal or oblique fields for the boost.

Results: Stage distribution was not significantly different between the ipsilateral and the bilaterally treated group (St. I: 0%/ 4% St. II: 23%/ 20% St III: 32%/ 31% and St. IV: 45%/ 46% respectively). There was a significant difference in xerostomia ($p<0.001$) with moderate or severe xerostomia in 52% of the unilateral treated and 89% of the bilateral treated patients. Dysphagia was significant or intense for 51% and 80% respectively. This result was also significant ($p<0.21$) in favor of unilateral treatment. In the unilateral treated group there was no nodal recurrence in the contralateral lymph node regions. There was 4 recurrences among the 31 unilaterally treated patients: One recurrence in the contralateral base of tongue in a patient with midline-structure involvement, one recurrence in primary involved N-site after CR, one PR at N site and one patient recurred with distant metastasis and out of field lymph node metastasis. These patients are dead from disease.

Conclusion: Unilateral radiotherapy of selected cancers in the tonsillary region seems safe concerning local control and survival and more lenient concerning xerostomia and dysphagia.

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Accelerated postoperative radiation therapy with weekly concomitant boost in patients with advanced head and neck cancer

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We wanted to assess the feasibility and efficacy of accelerated weekly 6 fractionated 66-Gy postoperative radiation therapy (PORT) using a single fraction regimen from Monday to Thursday and a concomitant boost in the Friday afternoon sessions in patients with advanced head and neck cancer (AHNC). Between December 1997 and June 2002, 89 (male to female ratio: 68/21; median age: 60 years [range: 36–81]) consecutive patients (refusing to participate or ineligible for the EORTC 22931 study comparing PORT vs. PORT plus chemotherapy) with pT1-pT4 and/or pN0-pN3 AHNC (28 oropharynx, 26 oral cavity, 18 hypopharynx, 6 larynx, 5 unknown primary, 4 salivary gland, and 2 paranasal sinus) were included in this prospective study. PORT was indicated because surgical margins were not free of tumor (n = 22) or for T4 tumors (n = 4) in 26 (29%) patients; or because of extranodal infiltration with (n = 33) or without (n = 30) positive surgical margins in 63 (71%) patients. Median interval between surgery and RT was 6 weeks (3-15). RT consisted of 66 Gy (2 Gy/fr.) in 51/2 weeks. Median RT duration was 39 days (range: 35-67). Prophylactic percutaneous endoscopic gastrostomy was applied in 26 (29%) patients. Median follow-up was 21 months (range: 2-59). All but one patient (not finishing the treatment because of non treatment-related reasons at 56 Gy) received the planned total dose without unplanned interruption. Acute morbidity was acceptable: grade 3 mucositis in 20 (22%) patients, grade 3 dysphagia in 22 (25%) patients, grade 3 skin erythema in 18 (20%) patients. Median weight loss of was 2 kg (range: 0-14.5). No grade 4 toxicity was observed. Considering the late effects, grade 0, 1, 2, or 3 xerostomia was observed in 15 (17%), 57 (64%), 11 (12%), and 6 (7%) patients, respectively; grade 0, 1, 2, and 3 edema in 29 (33%), 46 (52%), 12 (13%), and 2 (2%) patients, respectively. Median time to locoregional relapse was 10 months (range: 2-21); only 4 (4%) local and 9 (10%) regional relapses were observed, and 18 (20%) patients developed distant metastases (all locally controlled but with regional relapses in 4 cases). The 2-year overall, cause-specific, and disease-free survival rates were 70%, 75%, and 63%, respectively; and 2-year actuarial-local and locoregional control rates were 94% and 80%, respectively. Distant metastasis probabilities at 2 and 4 years were 20% and 38%, respectively. Univariate analyses revealed that pT-stage, 3 or more lymph node metastases, and extranodal extension in 2 or more lymph nodes were significant. Multivariate analysis (Cox model) revealed that pT-stage (pT1, 2 vs. pT3, 4) and extranodal extension (0, 1 vs. 2 or more) were the two factors independently influencing the outcome. We conclude that reducing the overall treatment time using accelerated PORT by weekly concomitant boost (6 fractions per week) is easily feasible with excellent local control. Acute and late RT-related morbidity is highly acceptable. Given the disease progression pattern (distant metastases), adjuvant chemotherapy should be considered.

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Late normal tissue sequelae and performance status with brachytherapy or surgery in tonsillar fossa and soft palate tumors. Can we be more selective?

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Background: This paper focuses on late normal tissue sequelae and functional performance in tonsillar fossa (TF) and soft palate (SP) tumors. Arguments are presented for a more selective treatment strategy while maintaining excellent tumor control.

Materials/Methods: From 1986-2001, T1-3 TF/SP tumors were treated by ERT to the primary and neck, followed by HDR-BT (primary tumor) and a neck dissection (ND) in case of N+ disease (BT-group; 104 patients). If BT is not feasible, surgery is performed with postoperative ERT (S-group; 86 patients). Local control (LC), regional control (RC), disease free survival (DFS) and overall survival (OS) were calculated according to Kaplan Meier. Late side effects are scored by RTOG criterion. Univariate (UV)- and multivariate (MV) Cox regression analyses were performed for regional failure (RF) and late mucosal side effects (ulcer), with parameters sex, age, site, T/N-stage, modality, dose, and OTT. To determine Performance Status Scores (PSS), a survey was conducted among patients alive and NED after a minimum of 2 years of FU (BT-group 30; S-group 27). A research nurse interviewed patients regarding eating in public (EPub), normalcy of diet (NDiet), understandability of speech (USpeech) and xerostomia (visual analogue score [VAS] and 4 validated queries).

Results: Control percentages BT vs. S: LC 88 vs.88, RC 93 vs.85, DFS 57 vs.52, OS 67 vs.57. MV-analysis for RF was significant for T2 vs.T3 (HR 0.09, 95% CI 0.01-0.83) and for dose neck > 46 Gy (HR 8.7, 95% CI 1.3-57.1). Late side effects BT vs. S: Ulcer 39% vs.7%, trismus 1% vs.21%. MV-analysis for ulceration was significant only for BT (HR 4.1, CI 1.6-10.5). Ulcers showed complete healing in 88% (median duration 6 months). Median PSS BT vs. S: EPub, 50 vs. 50 ($p=0.97$), NDiet, 50 vs. 60 ($p=0.89$), USpeech, 100 v. 75 ($p=0.34$). Xerostomia: median VAS 5.5 (BT; range 0-10) and 6 (S-group; range 2-10). In the majority of the BT (72%) and S (73%) patients the answers to the 4 standardized queries were associated with their xerostomia complaints.

Conclusions: Excellent LR control was obtained with either modality: 84% (BT) vs.78%(S). BT patients fared better in understandability of speech (100 vs. 75). Late side effects were not negligible (ulcer [BT], fibrosis / trismus [S], both groups being equally affected by xerostomia). Fortunately,