Results: 60 pts were enrolled into the trial. 85% of pts had metastatic disease. Median age was 45 years (range 23-64) and median KPS at entry was 90 (range 60-100). 53 pts received radiotherapy (RT alone 12 pts, RT/CT 41 pts) and all pts had received a palliative platinum-based therapy. Among 57 out of 60 (14 F, 46 M) pts who were evaluable for efficacy, there were 7 (12.5%) pts with confirmed partial responses (PR), 3 (5.4%) pts having an unconfirmed PR, and 26 (46.4%) pts with stable disease (SD). The clinical benefit (PR+SD) was 64.3%. Median duration of treatment received was 2.5 months. The median time to response was 1.37 months (range 1.27-2.70 months), the median time to progression was 5.70 months (range 4.43-7.23 months), and median overall survival (n=43) was 6.47 months (range 0.17-18.4). Safety profile: skin rash (91% any NCI/CTC grade, 8% grade 3-4), nausea & vomiting (89% any grade, 8% grade 3-4), asthenia (36% any grade, 5% grade 3-4), anemia (33% any grade, 21% grade 3-4), thrombocytopenia (24% any grade, 10% grade 3-4). No serious allergic reactions were encountered.

Conclusion: Cetuximab (Erbitux™) in combination with carboplatin has good activity and acceptable safety profile in heavily pretreated pts with R&M NPC who failed to platinum therapy.

678 ORAL

EGFr expression and histopathological differentiation influence the response to accelerated fractionation in squamous cell carcinomas of the head and neck (HNSCC). Analysis of 702 patients from the randomized DAHANCA 6 and 7 trial.

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Background: Accelerated fractionation of HNSCC results in improved tumor control compared to conventional schedules. However, the response may be heterogeneous and not all tumors benefit from such treatment. A previous study has indicated that poor histopathological differentiation and low expression of EGFr may compromise the ability of tumors to express accelerated regeneration.

Patients and material: 702 patients with available tissue blocks from the DAHANCA 6 & 7 trial were evaluated for tumor differentiation and EGFr expression using immunohistochemistry. Treatment was radiotherapy to a total dose of 66-68 Gy given with 2 Gy/fx. All patients were randomly assigned to receive this in either 5 or 6 fx/wk, resulting in an overall treatment time of 6.5 or 5.5 weeks, respectively. The primary endpoint was actuarial 5-year loco-regional control.

Results: Poor differentiation was observed in 236 (34%) patients and low EGFr in 112 (16%) patients. There was some correlation between poor differentiation and lack of EGFr but otherwise there was no correlation between these parameters and classical prognostic factors. As shown in the full DAHANCA 6 & 7 trial, acceleration in this cohort of patients resulted in a significant improved 5-year loco-regional control rate (53% vs. 66%, $p<0.001$ for 5 fx/wk or 6 fx/wk, respectively). There was no effect of acceleration in poorly differentiated tumors (57% vs. 64%, n.s.), whereas well to moderate differentiated tumors showed a significant benefit (50% vs. 67%, $p<0.001$). Similarly, there was no effect of acceleration in tumors with low expression of EGFr, whereas high expression was related to a better outcome in tumors treated with 6 fx/wk (53% vs. 65%, p=0.004). By combining the two parameters it was apparent that the presence of either low EGFr *or* poor differentiation, which was found in 294 patients, resulted in lack of response to acceleration (57% vs. 63%, n.s.), whereas the other 408 tumors with well to moderate differentiation *and* high EGFr showed a marked response to acceleration with loco-regional control rates of 49% vs. 67%, p=0.0005. Multivariate analysis confirms that acceleration has no influence on loco-regional control in tumors with low EGFr or poor differentiation, whereas it is the case for well to moderate differentiated tumors with high EGFr.

Conclusion: The study illustrates the complexity of EGFr: EGFr alone has no predictive value whereas the predictive value of EGFr in combination with tumor differentiation is dependent of the overall treatment time of radiotherapy. Tumor repopulation may be linked with factors influencing control of tumor differentiation and proliferation. Poor histopathological differentiation and lack of EGFr expression indicate that such mechanisms are not functioning. From that follows that the beneficial use of anti-EGFr drugs could be more limited than expected.

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679 ORAL

Pretreatment gene expression profiling value in predicting the clinical outcome of patients with oropharyngeal carcinoma

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Background: Individual tumors display a wide range of responses to radiotherapy and/or chemotherapy and consequently unpredictable outcome. The aim of the present study was to assess the predictive value of the pretreatment gene expression profiles of oropharyngeal squamous cell carcinomas.

Material and Methods: Twenty-six pretreatment biopsies from patients managed with radical radiotherapy were analyzed with microarrays containing 4132 cDNAs of human genes. Twelve from patients who were disease-free at a minimum follow-up of 12 months and 10 presenting with any event (locoregional or distant), while four patients served as a test.

Results: The selection of 738 genes expressing signal over background enabled the clustering of the whole group into two distinct groups according to their oncological outcome (with and without event). The profiles that best discriminate between the two groups are those from the first cluster of 11 genes, particularly 5 genes that showed a clear distinct pattern. To evaluate the predictive strength of the method, we examined 4 additional biopsies in a blind test and correctly predicted them to be in the disease-free group.

Conclusions: Pretreatment gene expression profiling represents a promising tool in predicting the clinical outcome of patients suffering from oropharyngeal squamous cell carcinoma and treated with radical radiotherapy.

680 ORAL

HPV infection as prognostic factor in squamous cell cancers (SCC) of oropharynx treated with surgery with or without radiotherapy (RT)

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Background: Head and neck squamous cell carcinomas (HNSCC) are generally associated with alcohol abuse and smoking, but for a subgroup of these tumors increasing data suggest a link to HPV infection. HPV positive (pos) oropharyngeal cancer seems to represent a distinct clinical entity. HPV pos cancers have been reported to have a better outcome although published series are heterogeneous in patient selection and treatment. Two studies showed a better radiosensitivity for HPV pos neoplasms. To verify the prognostic role of HPV infection in oropharyngeal SCC cancer we retrospectively analyzed a series of patients treated with surgery with or without RT.

Patients and Methods: Genomic DNA from paraffin embedded surgical samples of 55 patients treated at our Institution from April 1990 to June 1999 was extracted. The amount of HPV 16 and 18 DNA was analyzed by absolute quantitative PCR and then HPV16 pos cases were tested for E6 and E7 mRNA. Overall and cause-specific survival rates were tested according to Kaplan-Meier analysis.

Characteristics	HPV pos *n (%)*	HPV neg *n (%)*
Sex		
Male	7 (54)	34 (81)
Female	6 (46)	8 (19)
Median age (years)	58	57
Stage		
II-III	7 (54)	15 (36)
IV	6 (46)	27 (64)
Node status		
Negative	4 (31)	13 (31)
Positive	9 (69)	29 (69)
Site		
Tonsil	4 (31)	16 (38)
Base of tongue + GlossoTonsillar Sulcus	7 (54)	14 (33)
Other	2 (15)	12 (29)
Treatment		
Only surgery	4 (31)	17 (40)
Surgery plus radiotherapy	9 (69)	25 (60)
Relapse	4 (31)	23 (55)
Metachronous second tumors	0	5 (12)