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)

Results: see table. At 5 years cause specific survival is 69% for HPV pos group and 48% for HPV neg (p=0.047); overall survival is 69% and 43% respectively (p=0.007).

Conclusions: HPV pos SCCs of oropharynx confirm to have a better prognosis when surgery is the main treatment. On the contrary patients with HPV neg tumors are more susceptible of relapse and second tumors in upper aero digestive tract. These data add evidence to the hypothesis of a different pathogenesis among SCC oropharyngeal cancer implying possibly different therapeutic approaches as well as surveillance and prevention programs. *Supported in part by AIRC.*

681 ORAL

The FDG standardized uptake value in predicting the outcome in head and neck cancer patients

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Background: Pre-treatment 2-[18F] fluoro-2-deoxy-D-glucose (FDG) uptake was evaluated as a predictor of local control (LC) and disease-free survival (DFS) in patients with head and neck cancer managed primarily either by radiotherapy (RT) or surgery.

Methods: In 120 patients, tumour FDG uptake using the Standardised Uptake Value (SUV) was measured prospectively using positron emission tomography (PET). Treatment consisted of either radical RT with or without chemotherapy (73 patients) or radical surgery with or without post-operative RT (47 patients). The correlation of LC and DFS with the maximum SUV values and with the other clinical and therapeutic variables was assessed by using the Kaplan-Meier method for univariate analysis and the Cox proportional hazards model for the multivariate analysis. Median follow-up of the surviving patients was 48 months.

Results: In the 46 patients who failed treatment, the median SUV was higher than in the remaining patients (5.8 vs. 3.6, p = 0.002). In monovariate analysis, patients with tumours having high FDG uptake (SUV > median, 4.76) had poorer LC (p = 0.003) and DFS (p = 0.005). This difference was also observed when the RT and surgery groups were analysed separately. In the multivariate analysis T-category (p= 0.005) and SUV (p= 0.046) remained independent adverse factors for LC, whereas N-category (p= 0.004), T-category (p=0.02) and SUV (p= 0.05) were independent determinants of DFS.

Conclusions: This study suggests that pre-treatment tumour FDG uptake represents an independent prognostic factor in patients with head and neck cancers, whatever the primary treatment modality. Because the greater risk of failure, tumours having high FDG uptake should be considered for more aggressive multimodality therapy.

682 ORAL

Validation of CT-based Rotterdam/Brussels neck nodal delineation protocol cranial boundary of level II and relevance for sparing of the parotid gland

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Purpose: Image guided high-precision radiation therapy (RT) for H&N tumors is frequently dependent on the 3D definition and delineation of the to be irradiated neck nodal levels. *Rotterdam* and *Brussels* have recently proposed CT-based consensus guidelines for the neck, based on surgical levels as defined by the American Academy of Otolaryngology[1]. This paper specifically addresses the validation of the proposed cranial boundary of level II, that is the lateral process of vertebra C-I, given its relevance for sparing of the Parotid glands (PG).

Materials and Methods: Neck irradiation is not trivial, in particular because of the associated xerostomia[2]. The selection of patients, in which the neck is to be irradiated, is based on generally accepted conventions[3]. Preserving salivary flow is related to the volume of the glands receiving a below threshold dose. *Rotterdam* and *Brussels* have recently translated the surgical levels of the neck unto CT. To validate the proposed CT-based guidelines, in our integrated operative suite a CT scan was obtained of a patient undergoing a neck dissection (ND). Before removing the (non-) lymphatic structures, surgical clips were placed at specific boundaries of neck levels and important anatomical marker structures. 2 mm CT-slices were obtained in surgical position (twisted neck) as well as in RT treatment position (neck on RT base, head rectangular to tabletop). Additionally, validating the most cranial dissection margin (this paper), in 10 consecutive patients undergoing a ND, after placing a surgical clips at the cranial border of level IIB, AP- and lateral X-ray films were taken in the OR with the head in RT treatment position. Finally, 10 patients with a primary tumor in the tonsillar fossa were contoured on CT. The position of the cranial border of level IIB was varied 1cm above and below the consensus boundary and, using IMRT treatment techniques, dose volume histograms of the PG were generated.

Results: In general, the positions of the clips were consistent with the consensus guidelines. In a sagital reconstruction of a CT taken in surgical position, the clips of level IIB were visualized at the base of skull. In RT position they were found at the level of the lateral process of vertebra C-I on sagital CT-reconstruction as well as on the X-ray films (see panels below). The mean dose to the PG with the upper border of level IIB as proposed by the consensus guidelines was 25.6 Gy (16.0-30.9), at + 1 cm 30.8 Gy (20.8-37.1) and at -1cm 18.1 Gy (10.2-24.2).

Conclusion: The Rotterdam / Brussels CT-based neck consensus guidelines proposed the cranial boundary of level IIA/B to be at the level of the lateral process of vertebra C-I. The observed position of the clips in RT treatment position (CT, X-ray) proved the adequacy of this proposal. It is important to adhere to the proposed guideline, given the large impact of a small upward shift on the mean dose in the PG.

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683 ORAL

Integration of fractionated stereotactic radiation therapy into the management of nasopharyngeal carcinoma

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Background: The management of nasopharyngeal carcinoma (NPC) requires the delivery of high dose radiation in close proximity to numerous organs at risk. This report describes the use of fractionated stereotactic radiation therapy (FSRT) with conventional conformal radiation therapy (CRT) for the initial management of NPC.

Materials and Methods: A review of 87 patients with NPC treated between 1997 and 2002 was conducted. All patients were undergoing initial curative management with a combination of CRT and FSRT. The treatment approach delivered 70 Gy to the primary site, 60 Gy to involved nodes and 50 Gy to nodal regions at risk. FSRT was used to deliver the final 10 to 20 Gy to the primary site. In selected cases with advanced primary tumours and nodal disease, FSRT to the primary site was commenced earlier and delivered concurrently with CRT. FSRT was planned using pre-treatment MRI's fused to the stereotactic planning CT. The PTV included the pre-treatment CTV plus a margin of 3mm where possible.

Results: 63 males and 24 females with a median age of 52 (range:17-78) were treated. T categories were: T0(1), T1(29), T2a(7), T2b(10), T3(15) and T4(25). Nodal involvement was present in 63/87 (72%). Median follow up was 1.6 years (range: 0.3 - 5.2). Three FSRT techniques evolved sequentially:1) Radionics® XKnife® system of multiple arcing beams with circular collimation; 2) XPlan® system of multiple static beams defined by a minimultileaf collimator (MMLC) and finally 3) intensity modulated radiation therapy (IMRT) using the MMLC. The number of patients treated were: XKnife (18), XPlan (20) and IMRT (49). FSRT was delivered in three dose ranges: $\leq$ 10 Gy (45 patients), >10 $\leq$ 20 Gy (17 patients), >20 Gy