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

(25 patients). In the latter dose range the FSRT was partially delivered concurrently with the CRT. Concurrent chemotherapy was administered to 47% (41) and neoadjuvant chemotherapy to 4% (3) . Two year actuarial rates of overall survival and disease free survival were 98% and 83%. Local, nodal and distant control rates at 2 years were 86%, 98% and 94%. Two year local control rates by T category were: T1: 95%, T2A: 83%, T2B: 88%, T3:100%, T4: 66%. Means of the maximum point dose to brainstem and optic chiasm were 56% and 34% of the prescribed FSRT dose. FSRT delivered with IMRT allowed larger CTV's to be treated (median volumes: 48 ml IMRT, 38 ml XPlan, 37 ml XKnife) permitting the inclusion of involved retropharyngeal nodes in the volume treated with FSRT. No patients have developed significant late toxicity at the time of this review.

Conclusion: FSRT has been successfully integrated with CRT for the initial management of NPC. Coverage of larger volume tumours was better achieved with stereotactic IMRT than Xknife or XPlan. Sparing of critical normal structures without compromise of dose delivered to the tumour was achieved. A comparison of FSRT to CRT and large volume nonstereotactic IMRT will be presented.

684 ORAL

Radiotherapy combined with cisplatin, carboplatin, mitomycin C, and 5-FU single drug or two drug chemotherapy compared to radiotherapy alone in unresectable head and neck cancer - a meta-analysis

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Background: Former meta-analysis on the addition of chemotherapy to radiotherapy in unresectable squamous cell cancer of the head and neck showed a small but significant survival advantage in favour of simultaneous chemotherapy. However, the meta-analysis included studies with older bleomycin and MTX containing chemotherapies that are not longer considered standard and did not take into account differences in the fractionation schedules used in the studies. Therefore, we performed a meta-analysis based on published data on modern chemotherapeutic regimens in combination with different radiation schedules.

Methods: Randomised trials comparing radiotherapy alone with simultaneous or alternating chemo-radiotherapy using cisplatin, carboplatin, mitomycin C, and 5-FU as single drug or combinations of 5-FU with one of the other drugs were included into the analysis. Group I trials included studies with conventionally fractionated radiotherapy (CF-RT) with or without single drug simultaneous chemotherapy. Group II consisted of trials with CF-RT in combination with or without simultaneous two drug chemotherapies or CF-RT compared to alternating chemo-radiotherapy (two drugs). Group III analysed studies of hyperfractionated-accelerated radiotherapy (HFX/AFX-RT) compared to HFX/AFX-RT in combination with simultaneous single or two drug chemotherapy. Survival data were fitted to a log-normal distribution to assess differences in survival in the respective study. The mean difference in overall survival of the pooled data in groups I-III were estimated using a maximum likelihood method.

Results: 20 trials with a total of 3513 patients were included into the analysis. Group I, II, and III consisted of 7, 6, and 7 studies including 1229, 951, and 1333 patients, respectively. Single drug chemotherapy in combination with CF-RT (group I) resulted in a survival benefit of 18.8 months (14.6 - 23.7 months 95% CL) compared with CF-RT ($p<0.00001$). The use of two drug chemotherapy in combination with simultaneous or alternating CF-RT (group II) was associated with an 8.8 months (5.4 - 12.8 months 95% CL) survival advantage compared with CF-RT alone ($p<0.001$). HFX/AFX-RT in combination with single or two drug simultaneous chemotherapy (group III) resulted in a 12.1 months (8.9 - 15.9 months 95% CL) longer survival than HFX/AFX-RT alone ($p<0.0001$).

Conclusions: Cisplatin, carboplatin, mitomycin C, and 5-FU single drug or combinations of 5-FU with one of the other drugs combined with simultaneous radiotherapy leads to a profound survival benefit in unresectable head and neck cancer patients irrespective the fractionation schedule of the radiotherapy.

Symptom management/Quality of life

685 ORAL

A phase 3, randomized, double-blind, placebo-controlled study of darbepoetin alfa in patients (pts) with lymphoproliferative malignancies

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Background: Darbepoetin alfa (Aranesp®) is a unique erythropoietic protein that is safe and effective for treatment of chemotherapy-induced anaemia in pts with solid tumors. Results of a phase 2 study suggest that similar outcomes could be achieved in pts with lymphoproliferative malignancies (Hedenus et al, 2002). This confirmatory phase 3 study was designed to evaluate the efficacy and safety of darbepoetin alfa in pts with lymphoproliferative malignancies.

Methods: This multicenter, randomized, double-blind, placebo-controlled study was conducted in anaemic pts (haemoglobin [Hb] $\leq$ 11.0 g/dL) with lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma, or chronic lymphocytic leukaemia) or myeloma who were receiving chemotherapy. No lower limit for Hb concentrations or specific endogenous erythropoietin level requirement was specified at study entry. Pts were required to be red blood cell (RBC) transfusion-free in the 2 weeks before randomization. Pts (n = 349) were randomized to receive darbepoetin alfa 2.25 mcg/kg (n = 176) or placebo (n = 173) by subcutaneous injection once weekly for 12 weeks. Mean change in Hb was calculated by 2 methods: in the intent-to-treat (ITT) analysis, missing values were imputed by last value carried forward; in the completers analysis, missing values were not imputed and only those pts who had a week 13 Hb value were included. Both methods excluded values within 28 days of RBC transfusion.

Results: see table.

The treatment effect of darbepoetin alfa relative to placebo was evident regardless of baseline endogenous erythropoietin level. Efficacy profiles were consistent between pts with lymphoma and myeloma. Improvements in health-related quality of life were also associated with darbepoetin alfa. The overall safety profile of darbepoetin alfa was consistent with that expected for this pt population.

Conclusions: Darbepoetin alfa is well tolerated and effective in increasing haemoglobin and reducing transfusions across a broad population of anaemic pts with lymphoproliferative malignancies.

686 ORAL

Epoetin alfa rapidly increases hemoglobin levels in anemic cancer patients receiving chemotherapy: results from a meta-analysis of nine randomized, placebo-controlled studies

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Background: Because of the relatively short duration of chemotherapy, it is important that any concurrently administered anemia treatment affords a clinically meaningful and rapid increase in hemoglobin (Hb) level to assure optimal patient benefits, including preservation or improvement of quality of life (QOL). Results from two large, multicenter, prospective, open-label, non-randomized, community-based studies (Demetri 1998; Gabrilove 2001) in anemic cancer patients undergoing chemotherapy showed mean Hb increases of ~1 g/dL after 1 month and ~2 g/dL after 2 months of epoetin alfa therapy (mean baseline Hb, ~9.4 g/dL).

Methods: To further characterize the Hb response to epoetin alfa, Hb data were gleaned from 1,646 chemotherapy patients who had received epoetin alfa 150-300 IU/kg three times weekly or placebo in nine randomized studies,

Abstract 685 – Table

	Darbepoetin alfa (n=174)	Placebo (n=170)	
Kaplan-Meier Proportion (95% CI) achieving haemoglobin response[a]	60% (52, 68)	18% (12, 24)	<0.001
Kaplan-Meier Proportion (95% CI) achieving haematopoietic response[b]	65% (57,73)	24% (18, 31)	< 0.001
Mean change (SE) in Hb (g/dL) from baseline to end of treatment (ITT analysis)	1.80 (0.17)	0.19 (0.10)	< 0.001
Mean change (SE) in Hb (g/dL) from baseline at 12 weeks (completers analysis)	2.66 (0.20) (n = 94)	0.69 (0.14) (n = 86)	< 0.001
Incidence (95% CI) of RBC transfusions from week 5 to end of treatment	31% (24, 38) (n = 167)	48% (41, 56) (n = 165)	< 0.001

[a] Increase of * 2.0 g/dL from baseline in the absence of RBC transfusions [b] Increase of * 2.0 g/dL from baseline or a haemoglobin value * 12.0 g/dL in the absence of RBC transfusions