has also been involved in cell proliferation and apoptosis. We tested in this study whether the polymorphisms of the glutathione *GSTM1*, *GSTT1* and G*STP1* might alter the risk for ovarian carcinoma (OC).
Material and Methods: Genomic DNA from peripheral blood of 137 consecutive OC patients and 137 controls were analysed by the multiplex-PCR for identification of the *GSTM1* and *GSTT1* genotypes and PCR-RFLP for identification of genotypes of the *GSTP1*. The differences between groups were analysed by χ^2 or Fisher exact test. Multivariate analysis served to obtain age and ethnic origin adjusted crude odds ratios (ORs).
Results: Similar frequencies of the *GSTM1* (37.6% versus 31.4%, $P = 0.37$) and *GSTT1* (30.6% versus 24.8%, $P = 0.25$) null genotypes were seen in patients and controls. In contrast, the *GSTP1* Ile/Ile genotype was more frequent in patients than in controls (59.1% versus 44.5%, $P = 0.01$). Individuals with this genotype had a 1.84 (95% CI: 1.14−3.01) fold increased risk for the disease. The frequency of the combined *GSTM1* null and *GSTP1* Ile/Ile genotypes was higher in patients than in controls (43.5% versus 24.6%; $P = 0.02$). Carriers of the genotype were under a 2.59 (95% CI: 1.18−5.64) fold increased risk for OC than others. Moreover, an excess of the *GSTM1* null, *GSTT1* null and *GSTP1* Ile/Ile combined genotype was seen in patients compared to controls (30.3% versus 7.1%; $P = 0.01$). Individuals with the genotype had a 8.00 (95% CI: 1.77−35.87) fold increased risk for OC than carriers of the remaining genotypes.
Conclusions: The results suggest that the variant *GSTT1*/*GSTM1* null and *GSTP1* Ile/Ile genotypes combination are linked to a substantial increased risk of development of OC. We hypothesised that *GSTT1* and *GSTM1* null genotypes leads to a loss of enzymatic conjugation activity, favouring the exposure of ovarian to estrogens. Apart from that, the *GSTP1* Ile/Ile genotype may add OC risk through different effects on cell cycle by protecting cells against apoptosis promoting tumour cells survival.
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Head and neck cancer

Oral presentations (Tue, 22 Sep, 14:45−16:30)
Head and neck cancer

8500 ORAL

Expression of EGFR and HPV-associated p16 in head and neck cancer: correlation and influence on prognosis after radiotherapy in 1088 patients from the randomised DAHANCA 5, 6 & 7 trials

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Background: Expression of p16 is highly correlated to infection with Human Papillomavirus in squamous cell carcinoma of the head and neck (HNSCC). Previous reports have demonstrated an inverse correlation between expression of epidermal growth factor receptor (EGFR) and p16 in HNSCC. The aim of this study was to examine the correlation between EGFR and p16 and to asses their influence on response to radiotherapy (RT) and survival in a large cohort of HNSCC patients treated with RT alone in the randomised DAHANCA 5, 6 & 7 trials.
Material and Methods: Between January 1986 and December 1999 The Danish Head and Neck Cancer group (DAHANCA) conducted the nationwide DAHANCA 5, 6 & 7 randomised trials, focusing on overcoming the disadvantages of tumour cell hypoxia and accelerated tumour cell proliferation in relation to RT. In the present study 1088 pre-treatment tumour tissues from patients in these trials were examined by immunohistochemistry for EGFR-expression (high/low) and p16 status (pos/neg).
Results: In total 258 of 1088 (24%) tumours were p16pos and 885 (81%) had high EGFR-expression. The correlation between EGFR and p16 was found to be inverse with p16pos tumours tending to have lower EGFR-expression (27%) compared to p16neg tumours (16%, $p < 0.0001$). In the oro-pharynx the frequency of p16 was highest (132/329, 40%) and the inverse correlation between EGFR and p16 most pronounced (63% of tumours with low EGFR were p16pos). Prognosis was significantly improved for p16pos tumours compared to p16neg: loco-regional tumour control (66% vs 51%, $p < 0.0001$), disease specific survival (75% vs 58%, $p < 0.0001$) and overall survival (59% vs 41%, $p < 0.0001$) at 5 years. In multivariate analysis p16 remained an independent prognostic factor for loco-regional tumour control [OR: 0.49 (95% CI 0.38−0.62)], cancer specific death [OR: 0.43 (0.33−0.56)] and overall death [OR: 0.52 (0.43−0.63)]. EGFR-expression did not influence on prognosis, neither in the total cohort nor in subgroup analysis stratified by p16 status.
Conclusions: In this large cohort of patients with HNSCC treated with RT alone HPV-associated p16pos tumours had lower expression of EGFR than p16neg tumours. p16 status was found to have major prognostic impact on outcome after RT whereas EGFR-expression had no prognostic implication on its own and did not contribute to a refinement of the prognostic value of p16 status.
Presented on behalf of the Danish Head and Neck Cancer group (DAHANCA)

8501 ORAL

Larynx preservation using induction chemotherapy followed by radiation – five-year evaluation of swallowing and laryngeal functions for patients enrolled in the GORTEC 2000−01 randomized study

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Background: Larynx preservation, using induction chemotherapy followed by radiation or concomitant chemoradiation, could be achieved for patients with locally advanced larynx and hypopharynx tumors. However this kind of approach should cure the patient but also keep the function. The objective of this prospective study was to evaluate the 5-year functional results, focused on voice and swallowing, for patients treated with induction chemotherapy followed by radiation.
Materials and Methods: 213 patients have been enrolled in the GORTEC 2000−01 randomized study which compared induction chemotherapy with Cisplatin (P) and 5 Fluorouracil (F) with or without Docetaxel (T) followed by radiation in case of good response. Radiation therapy was proposed for 142 patients. The others were treated with total laryngectomy and post operative radiotherapy. With 61 months median follow-up, 67/142 are alive with their larynx. Questionnaires have been sended to all of these patient. The quality of the voice was evaluated using the “Voice handicap index 30” (VHI30). The impact on quality of life and swallowing function were assessed through the EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the “Quality of Life Head and Neck module” (QLQ-H N 35).
Results: 61 patients (91%) answered to questionnaires. Voice disability is very low for 57% of patients (VHI score <30) moderate for 28% (VHI score 30 to 60) and severe for 15% (VHI score >60). 1 patient have permanent tracheostoma. Mulivariate analysis has been done to test potential factors that would affect the results of the VHI. Recovering larynx mobilty following induction chemotherapy was the only predictive factor for a good VHI score ($p = 0.035$). The VHI score was correlated with the global quality of life scale and functional scales of the QLQ C 30. 25 patients (40%) had no eating or swallowing problems (eating HN35 score = 0). 17 patients (27%) used daily nutritional supplements and 5 patients (8%) had an enteral feeding tube. Patients who received induction chemotherapy with PF are taking more opioid treatments and nutritional supplements compared to those who received th TPF regimen.
Conclusions: Using induction chemotherapy followed by radiation for larynx preservation the quality of the functional result regarding voice was poor for 15% of the patients and for 8% of the patients regarding the swallowing function. These data would be useful for designing the future larynx preservation trials.

8502 ORAL

Long term (Five-year) results of Tax324: A Phase III Trial of Sequential Therapy comparing TPF with PF in Patients with locally advanced squamous cell cancer of the head and neck

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Background: In the original TAX324 report, after a minimum follow up of two years and a median of 42 months, sequential chemotherapy with Taxotere, cisplatin and 5FU (TPF) significantly improved survival by 30% compared with cisplatin and 5FU (PF). TAX324 and TAX 323 established Induction and Sequential therapy with TPF as treatment standards for patients with Locally Advanced Head and Neck Cancer (LAHNC). We are now presenting the long term results of the TAX324 study.
Material and Methods: After IRB approval, the study group used the anonymous study codes of the patients who were alive or lost to follow

up in the 2005 analysis to gather current data from the study sites. With a minimum follow up through December 1, 2008, data on survival, progression free survival and other factors were gathered and analyzed by summary statistics.
Results: The initial demographics, therapy and toxicity were previously reported. Data of 85% of 501 subjects randomized to either TPF or PF treatment on TAX 324 was collected. With a median follow up of 71 months and a minimum of 5 years, the overall survival in the TPF group was significantly longer than in the PF group (HR 0.74; 95% CI 0.58−0.94; p = 0.013). Median survival was 71 and 30 months respectively, and mortality was reduced 24% in the TPF arm compared with PF. At 5 years 52% and 42% of the TPF and PF patients are alive (p = 0.06). Subset analysis showed that the median survival was improved across all sites with TPF. Median survival was not reached in patients with oropharyngeal tumor locations who were treated with TPF while it was 68 months in the PF group (HR 0.71, 95% CI 0.5−1.97; p = 0.07). The complete data set including the rate of tracheostomy and enteral feeding tube dependence among survivors will be presented at the meeting.
Conclusion: The benefit of induction chemotherapy with TPF is significantly superior to PF beyond 5 years and has been maintained at essentially the same level of impact as in the 2 year follow up. These data support the long term efficacy of TPF and sequential therapy in the management of appropriate patients with locally advanced head and neck cancer.

8503 ORAL

Final report of NPC-9901trial on therapeutic gain and late toxicities attributed to concurrent-adjuvant chemotherapy for T1−4N2−3M0 nasopharyngeal carcinoma

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Purpose: The NPC-9901 Trial aims to evaluate the therapeutic ratio achieved by concurrent–adjuvant chemoradiotherapy (CRT) for regionally advanced nasopharyngeal carcinoma (NPC). This is the first trial with long term data on late toxicities in addition to survival rates.
Patients and Methods: Eligible patients with non-keratinizing NPC staged T1−4N2−3M0 were randomly assigned to radiotherapy (RT) alone or CRT. Both arms used the same RT technique and dose in line with the policy adopted by individual centers, all patients were treated with conventional fractionation to a total dose $\geqslant$ 66 Gy. Those in the CRT arm were given the Intergroup-0099 Regimen of cisplatin 100 mg/m^2 every 3 weeks for 3 cycles in concurrence with RT, followed by 3 adjuvant cycle of cisplatin 80 mg/m^2 and 5-fluorouracil 1000 mg/m^2/day for 96 hours every 4 weeks. All analyses were based on intention-to-treat principle.
Results: From March 1999 to January 2004, 348 patients have been accrued: 176 were randomized to RT and 172 to CRT. The median follow-up was 5.9 years. The 2 arms were well-balanced in all prognostic factors and RT parameters. The tumor control and late toxicity rates were listed in the attached Table.
Conclusions: Long term data confirmed that CRT could achieve significant improvement in progression-free survival due largely to improvement in locoregional control, but the benefits in distant control and overall survival did not reach statistical significance. No significant excess in overall late toxicity rate (Grade $\geqslant$3) was observed.

Comparison of Chemoradiotherapy versus Radiotherapy alone

Endpoint	Comparison of actuarial rate by log-rank test		Independent significance of CRT by multivariate analyses	
	5-year rate (%)	*P* value	Hazard Ratio (95% CI)	*P* value
Loco-regional control	88 *vs* 78	0.005	0.45 (0.25, 0.79)	0.006
Distant control	74 *vs* 68	0.319	0.82 (0.56, 1.21)	0.32
Failure-free rate	67 *vs* 55	0.014	0.66 (0.47, 0.92)	0.015
Progression-free survival	62 *vs* 53	0.035	0.72 (0.53, 0.98)	0.036
Overall survival	69 *vs* 64	0.188	0.79 (0.57, 1.12)	0.189
Late toxicity (Grade $\geqslant$3)	30 *vs* 21	0.205	1.29 (0.87, 1.93)	0.206

8504 ORAL

Induction chemotherapy (IC) followed by concomitant chemoradiotherapy (CCRT) versus CCRT alone in patients with locally advanced nasopharyngeal carcinoma (LA-NPC) – a randomized phase II study of the Hellenic Cooperative Oncology Group

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Background: CCRT is considered standard treatment in LA-NPC. The role of IC when followed by CCRT in improving locoregional control remains controversial.
Patients and Methods: 141 eligible patients with LA-NPC were randomized to either 3 cycles of IC with cisplatin (175 mg/m^2), epirubicin (75 mg/m^2) and paclitaxel (75 mg/m^2) (CEP) every 3 weeks followed by definitive radiotherapy (70 Gy) and concomitant weekly cisplatin (40 mg/m^2) (group A, 72 patients) or CCRT alone (group B, 69 patients). For the present analysis, p16, MAP-Tau and ERCC1 protein expression were assessed centrally in tissue microarrays by immunohistochemistry in 107 tumors. EBER status was investigated by in situ hybridization.
Results: 66 patients (92%) in group A received 3 cycles of IC. Totally, 89% of patients (86% in group A vs 93% in group B, p = 0.718) completed treatment as planned. The two groups were balanced in terms of age, gender, PS, stage, and histology (WHO). Overall response rate (ORR), the primary endpoint, was 78% in both groups. Complete response rate was 57% in group A and 52% in group B (p = 0.614). Most frequently reported severe toxicities included neutropenia (3% vs 6%), leukopenia (24% vs 29%), thrombocytopenia (17% vs 1%, p = 0.005), nausea/vomiting (20% vs 19%) stomatitis (30% vs 38%), dysphagia (15% vs 6%), and weight loss (25% vs 26%). After a median follow-up of 31 months, 26 patients progressed (10 vs 16) and 28 (12 vs 16) died. 1-year PFS rate was 84% and 70% in groups A and B, respectively (p = 0.006). p16, MAP-Tau and ERCC1 protein expression was reported in 4%, 44% and 49%, respectively. EBER positivity was recorded in 67 out of 76 patients (88%) with type III, 18 out of 22 patients (82%) with type II and 3 out of 9 patients with type I histology (p = 0.001). No biological marker was associated with tumor response.
Conclusions: ORR with the CEP regimen followed by CCRT is not superior compared to CCRT alone in patients with LA-NPC. None of the biological markers investigated was of predictive value. Follow-up is continued to obtain further information on the type of progression and survival.

8505 ORAL

RapidArc for locally advanced head and neck cancer – first clinical results

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Background: Volumetric modulated arc radiotherapy is of upcoming interest instead of classical standard IMRT for treating locally advanced head and neck squamous cell carcinoma (HNSCC). For the first time we present clinical data regarding acute toxicity for a cohort of 40 patients (pt) treated with RapidArc (RA, Varian Medical Systems) with a simultaneous integrated boost (SIB) technique.
Material and Methods: From June 2008 until March 2009 40 pt with HNSCC completed RA treatment with curative intend. Primary tumor was located in the oropharynx (60%), hypopharynx and larynx (22.5%), nasopharynx (10%), paranasal sinus (5%) and nasal cavity (2.5%). Thirty pt were staged as AJCC stage III or higher, 10 pt were staged as I or II. Concurrent systemic therapy (cisplatin, cetuximab) was applied in 22 cases. Dose prescription was set at 70 Gy (2 Gy/fraction) for the primary tumor an pathological lymph nodes deliver as a SIB. The elective lymph nodes recieved a dose of 54.25 Gy (1.55 Gy/fraction) in an accelerated scheme (6 times a week, total treatment time 6 weeks) or 57.75 Gy (1.65 Gy/fraction) in a conventional setting (5 times a week, total treatment time 7 weeks). All patients were treated with two complementary arcs to optimize PTV homogeneity (Verbrakel et al, IJROBP 2009). Acute toxicity was recorded weekly according to RTOG Radiation Morbidity Scoring Criteria for dermatitis (D), mucositis (M), xerostomia (X), dysphagia (D) and laryngitis (L) and analyzed by the end of therapy. Results were compared retrospectively with recently published data from our patients treated using 7 field IMRT with sliding window technique (Vergeer et al, IJROBP 2009).
Results: All patients completed treatment as planned. S,M,D,L grade 3 or higher appeared in 32.5% and 12.3% (RA/IMRT), 30% and 18%, 50% and