

Results: In the lipoplatin arm, a total of 16 patients are evaluable after at least 2 cycles, while 14 patients are evaluable in the cisplatin arm. Demographic data are as follows: Men n = 27 (age 45–74 y, mean 55.5 y), women n = 2 (ages 47 y and 64 y). Haematotoxicity was more frequent in the cisplatin arm with leucopenia grade I/II in 7 cases and grade III/IV in 2 cases, while only 2 patients developed leucopenia (grades I/II) in the lipoplatin arm. Anemia was shown in either therapy arms: cisplatin and lipoplatin grade I: 2 pts and 4 pts, resp; grade II: 6 pts and 3 pts, resp; grade III: 2 pts and 2 pts, resp. Furthermore, 2 patients in the lipoplatin arm experienced renal toxicity of grade I as measured by a reduction of the creatinine clearance, while 6 patients showed a decrease of grade 2. Renal toxicity increased to 10 patients in the cisplatin arm (grade I: 4 pts; grade II: 4 pts; grade III: 4 pts). One case of ototoxicity occurred in the lipoplatin arm (grade IV) in contrast to 5 cases in the cisplatin arm (of grade II each). During cisplatin chemotherapy, 4 patients presented with grade I neurotoxicity, whereas only 2 patients developed neurotoxicity of grades I and III, each, in the lipoplatin arm.

Conclusion: Lipoplatin seems to reduce both the haematological and non-hematological toxicity profiles of cisplatin to a clinically relevant extent when combined with 5-FU. Because patients with advanced SCCN have an increased risk of renal toxicity due to poor hydration, the observed reduction of side effects will influence the chance to preserve the dose density of chemotherapy, and thereby, the efficacy of treatment.

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ORAL

Results of Intensity Modulated Radiotherapy (IMRT) in laryngeal and hypopharyngeal cancer: A dose escalation study

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Background: A study designed to determine the toxicity of dose-escalated IMRT using an accelerated RT schedule with concomitant chemotherapy.

Methods: Patients with T2–4, N1–3, M0 squamous cell carcinoma of the larynx or hypopharynx were recruited. A single-phase inverse-planned simultaneous boost was delivered by IMRT. In the first cohort 63 Gy/28F(daily) were delivered to the primary tumour and involved nodes and 51.8 Gy/28F to the elective nodal areas with concomitant Cisplatin, 100 mg/m² w1&5.

In cohort2, the primary tumour and involved nodes were dose escalated to 67.2 Gy/28F. Acute (NCICTCv2.0) and late toxicity (RTOG and modified LENT SOM) was collected.

Results: 30 patients were entered, 15 in each cohort. For cohort 1, median age was 57 y(35–75), 9 larynx/6 hypopharynx. Complete response(CR) rate was 87%, with 13% partial response(PR) rate. At median follow up(FU) of 19 months(range 12–33), local recurrence occurred in 6 patients(40%): 5 in the high dose volume and 1 in the elective neck. Overall survival(OS) was 73% with a laryngeal preservation rate in the surviving patients of 82%. For cohort 2, median age was 66 y(60–85), 6 larynx/9 hypopharynx, and median FU 6 m(1–11). CR rate was 87% and PR 13%. No grade 4 toxicity was observed.

Acute toxicity is summarized in table 1. The typical pattern of radiation dermatitis observed was one of widespread erythema with dry and/or moist desquamation over the neck creases, which by week 4 post-RT had mostly settled, with 80% in cohort 1 and 85% in 2 having no toxicity at week4 post-RT. In cohort 1, 93% patients had dysphagia grade ≤2 by week 8 post-RT and 73% in cohort 2. G ≤1 pain was experienced by 93% patients by week 8 post-RT in cohort 1 and 82% in cohort 2.

Table 1: Grade 3 NCI CTC v2.0 acute toxicity

	Cohort 1	Cohort 2
Radiation dermatitis	20%	15%
Dysphagia	60%	87%
Pain	30%	40%
Mucositis	47%	33%
Xerostomia	0%	7%

No severe late toxicity was seen in 87% patients. In cohort 1, 1 patient had G3 hoarseness at 18 m and 1 had G3 dysphagia at 6m that resolved to G1 by 1 y. At 1 y, 90% had xerostomia G0–1(LENT SOM). Maximum EORTC late toxicities were G2 dysphagia in 1 patient and G2 xerostomia in another. In cohort 2, 1 patient had G3 laryngeal toxicity and 1 G3 dysphagia at 6 m and 90% had xerostomia G0–1(LENT SOM). Maximum EORTC late

toxicities at 6m were G3 dysphagia in 1 patient and G2 laryngeal toxicity in 2 patients.

Conclusions: Initial results of dose escalation with chemo-IMRT suggest high CR, OS and laryngeal preservation rates. Acute toxicity shows recovery over time and initial late toxicity is rare. Longer follow up is required to determine the incidence of late side effects.

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ORAL

Longitudinal changes in quality of life and costs in long-term survivors of tumors of the oropharynx treated with brachytherapy or surgery

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Purpose: To assess the longitudinal changes in quality of life (QOL) and treatment costs in long-term survivors of oropharyngeal cancers treated with brachytherapy (BT) or surgery (S).

Materials and Methods: From 1991–2001, 144 patients with tonsillar fossa (TF) and/or soft palate (SP), and base of tongue (BOT) tumors, were treated by organ function preservation therapy, using external beam radiotherapy (EBRT) and BT. 110 patients not suitable for BT were treated by a combined resection with postoperative EBRT. Among all patients ≥2 and <10 years alive NED, a QOL survey was conducted in 2003 and repeated in 2005. Two groups were studied: group I TF/SP/BOT tumors treated by S (44), and group II TF/SP/BOT tumors treated by BT (75). The performance status scales scores for eating in public (EP), understandability of speech (SP), and normalcy of diet (ND) were determined. In addition, xerostomia ("dry mouth") and the (in)ability to swallow ("drink to eat"), were measured by standardized queries and a visual analogue scale. By regression analysis, the effect of time from diagnosis, age, dose, sex, T/N-stage, trismus, necrosis and treatment modality on the PSS scores was determined. 22 Patients of group I, and 27 of group II were eligible for analysis. In conjunction with the 2005 survey, the EORTC QLQ-C30, EORTC H&N35, and Euroqol (EQ5D) questionnaires were mailed. For each treatment group treatment costs were computed.

Results: In the 2003 survey EP, SP, and ND showed significant difference in BT as opposed to S. Over time, a significant difference was found for drink to eat and for ND for BT as opposed to S. For the QLQ-H&N35: S patients experience significantly more speech, teeth and opening mouth problems. Parameters significantly effecting the mean QoL scores were age, total dose, sex, trismus and treatment modality.

Mean costs: group I: €26,590, and group II: €16,112.

Discussion: The QOL surveys of this paper show that item for item the median scores did not significantly change in time. For each group, discriminating factors seem to be modality related and site specific (e.g. BT more ulceration, surgery more trismus, and for both modalities the dry mouth syndrome). Due to the number of admission days, S is more expensive as opposed to BT. Given the good tumor control for both treatment groups (BT and S); 85% at 10 years, the data suggest that QOL and associated costs, can be of additional value when discriminating between treatment modalities.

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ORAL

The Chernobyl legacy: relationship between radiation exposure, RET rearrangement and BRAF mutation in childhood thyroid cancer

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There was a large increase in the incidence of papillary thyroid cancer in those areas of Ukraine exposed to radioactive fallout following the Chernobyl Nuclear Power Plant accident in April 1986. This increase was most pronounced in those who were children at the time of the accident. Thyroid cancer is usually very rare in children (aged under 16 at operation). 131-I has a relatively short physical half-life (7 days) and the rate of thyroid cancer has dropped back to background levels (of the order of 1 per million per year) in those who were born after 1st January 1987. The Chernobyl Tissue Bank (www.chernobyltissuebank.com) was established in 1998 to collect biological samples from those aged under 19 (i.e. born after 26th April 1967) at the time of the accident who subsequently developed thyroid tumours and were resident in the areas of Ukraine and Russia most highly contaminated by radioiodine in fallout. The continued collection of material has allowed us to collect samples from children from the same geographical area, but born more than 9 months after the accident, and whose thyroid cancer therefore is not the result of exposure to radioiodine. This is a unique

situation that provides the opportunity to link molecular biology of cancer with a known environmental exposure to a mutagen.

The aim of this study was to investigate whether the frequency of ret rearrangement and BRAF mutation in papillary carcinoma of the thyroid (PTC) is related to exposure to radiation or the age of the patient at clinical diagnosis. RNA extracted from 52 cases of PTC were obtained from the Chernobyl Tissue Bank. The cases were divided into 4 groups matched on age, sex and place of residence. Two groups of 13 cases were from the areas of Ukraine most heavily contaminated with radioiodine, one group was born before the accident (1A), and the other born after 1/1/87 (1B) and therefore not exposed to radioiodine. Two other groups of 13 cases were from areas of Ukraine not exposed to significant fallout, one born before the accident (2A) and the other after 1/1/87 (2B). All patients were aged under 16 at the time of operation. The expression of ret was determined by RT-PCR for the extracellular and intracellular regions of c-ret [1] and PTC1 and 3 rearrangements were identified by rearrangement specific RT-PCR. For BRAF, mutation at position 1746 was identified by PCR followed by restriction enzyme digestion [1].

There was no significant difference among the groups with respect to type or overall frequency of ret rearrangement. The most frequent rearrangement was PTC3, accounting for 16 of the 25 cases positive for ret rearrangement. Only one case (in group 2B) was positive for BRAF rearrangement. This study shows that contrary to other reports in the literature, there is no association of either ret rearrangement per se, or PTC3 rearrangement in particular, with radiation exposure. Thyroid cancer presenting in adults is typified by a higher frequency of BRAF mutation (58% in a series from Ukraine). We suggest that the pattern of molecular biological alterations observed in post Chernobyl thyroid cancer is related to the age of the patients under study, rather than to exposure to radioiodine. The Chernobyl experience suggests that age at diagnosis should be taken into account before conclusions are drawn regarding the relationship between molecular biology and radiation. This has implications for current studies in breast cancer following radiotherapy for Hodgkin's Disease.

References

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Poster presentations (Tue, 1 Nov)

Head and neck and endocrine cancer

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POSTER

Intensity modulation radiotherapy for nasopharyngeal carcinoma – an experience in Taiwan

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Introduction: To present the treatment result of intensity modulation radiotherapy (IMRT) in nasopharyngeal carcinoma (NPC) by intensity modulation radiotherapy technique and concomitant chemoradiotherapy.

Patients and methods: There were 180 consecutive M0 NPC patients received IMRT from March 2000 and December 2003. The median age was 48 (13–84). One hundred and thirty one patients were male. All patients received H&N MRI to evaluate the local and regional tumor extension and 126 patients received FDG-PET before radical treatment. The stage distribution was stage I: 7; stage II: 67; stage III: 55 and stage IV 51. The gross tumor volume is defined based on the MRI T1 enhanced image with reference of FDG-PET image. Initial clinical tumor volume is defined as gross tumor volume with 1 cm margins and whole neck. The boost clinical tumor volume is defined as primary tumor and initial gross neck node with 0.5 cm margins. Planning volume is defined as clinical tumor volume with 0.3 cm margins. The IMRT planning is planned by commercial planning system with co-planar 7 fields technique. The radiation dose was 72 Gy to T1-T3 gross tumor area and 76 Gy to T4 lesion. The radiation was delivered by 2 Gy per fraction and 5 fractions per week. The maximal radiation dose <110% and no simultaneous boost was used. Stage IIb to IVb patients received concomitant chemotherapy with cisplatin, UFUR and leucovorin in outpatient clinic service. All patients with at least 16 months follow up or to death. The median follow up was 2.1 years.

Result: The 3 year overall survival (OS) was 91.7%. 3-year OS for stage I, II, III and IV was 100%, 100%, 91.7% and 80.6% respectively. There were 4 patients with local recurrence, 6 patients neck node recurrence and 12 patients with distant metastasis. The local tumor progression free rate for T1, T2, T3 and T4 was 100%, 96.3%, 92.3% and 90.4%. The 3-year distant metastasis free survival was 86.8%. There were no grade IV complications

were noted. 2-year grade II xerostomia according to RTOG criteria was 14%.

Conclusion: With combined use of IMRT, concomitant chemotherapy and through staging workup can get good tumor control and survival.

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POSTER

Neoadjuvant docetaxel (Taxotere) and cisplatin followed by concurrent cisplatin-radiotherapy in locally advanced nasopharyngeal carcinoma: a randomized phase II study

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Background: The current standard treatment for locally advanced nasopharyngeal carcinoma (NPC) is concurrent chemotherapy and radiotherapy (RT) (JNCI 2005; 97: 536–9). The current study aimed to compare the toxicities and tumor response of advanced NPC patients treated with concurrent cisplatin-RT +/- neoadjuvant docetaxel and cisplatin.

Methods: Previously untreated NPC of UICC 1997 stage III/IVA/IVB. Randomized (stratified by stage 3 vs 4) to one of two arms: (1) Neoadjuvant chemotherapy arm: docetaxel 75 mg/m² on D1 and cisplatin 75 mg/m² on D1 q 3 wks x 2 cycles, followed by cisplatin 40 mg/m² weekly x 6–8 weeks concurrent with RT (66 Gy in 2-Gy fractions), or (2) Control arm: concurrent cisplatin-RT as arm 1 without neoadjuvant chemotherapy. All treatments were delivered as outpatients. Planned accrual was 30 patients (pts) per arm to detect 20% difference of toxicity on one side of a 95% confidence interval.

Results: 60 pts were randomized from 11/2002 to 11/2004. Toxicity and response data of the first 53 pts were complete for this analysis (complete data for all 60 pts will be available at meeting). NCI-CTC grade 3 and 4 toxicities in the two arms were summarized in Table 1. All pts in the neoadjuvant arm completed the planned two cycles of chemotherapy and all pts in both arms completed RT to the prescribed dose. In the neoadjuvant arm, 86%, 71%, 43%, 7%, 3% completed 4, 5, 6, 7 and 8 weeks of concurrent cisplatin during RT. The corresponding numbers for control arm were 84%, 76%, 48%, 20%, 0%. Response rate to neoadjuvant chemotherapy: nasopharynx (NP) 86% (CR 22%, PR 64%), nodal 80% (CR 50%, PR 30%). Response after cisplatin-RT: (a) neoadjuvant arm: NP 100% (CR 96%, PR 4%), nodal 95% (CR 80%, PR 15%); (b) control arm: NP 100% (CR 84%, PR 16%), nodal 100% (CR 65%, PR 35%).

Conclusions: Neoadjuvant docetaxel and cisplatin was well tolerated and produced high response rate. The higher haematological toxicities in the neoadjuvant arm were manageable and did not compromise the delivery of full dose concurrent cisplatin-RT. This neoadjuvant strategy warrants a phase 3 study to determine its impact on the overall survival in advanced NPC.

Table 1: NCI-CTC Grade 3 and 4 toxicities during treatment.

	Neoadjuvant arm (n = 28)		Control arm (n = 25)		P-value
	G3	G4	G3	G4	
(a) During neoadjuvant chemotherapy					
Hematological					
Neutropenia	6 (21%)	21 (75%)			
Febrile Neutropenia	4 (14%)	0			
Non-haematological:					
Fatigue	2 (7%)	0			
Nausea/Vomiting	3 (11%)	0			
(b) During cisplatin-RT					
Hematological					
Anaemia	3 (10%)	0	5 (20%)	0	0.31
Thrombocytopenia	1 (4%)	1 (4%)	0	1 (4%)	0.11
Neutropenia	6 (21%)	22 (79%)	3 (12%)	1 (4%)	<0.0001
Febrile neutropenia	0	0	1 (4%)	0	0.29
Non-hematological					
Anorexia/nausea/vomiting	3 (10%)	0	3 (12%)	0	0.36
Dehydration/renal	5 (18%)	0	7 (28%)	0	0.58
Fatigue	2 (7%)	0	2 (8%)	0	0.91
Electrolytes	4 (14%)	0	0	0	0.07
Mucositis/odynophagia	10 (36%)	1 (4%)	11 (44%)	1 (4%)	0.24
Transfusion	4 (14%)	0	4 (16%)	0	0.86