surgical margins, 3 or more positive lymph nodes, or extranodal infiltration. Median interval between surgery and RT was 46 days (range: 24–112). RT consisted of 66 Gy (2 Gy/fr) in 5.5 weeks. Median RT duration was 39 days (range: 35−62). Five-field 3D conformal or intensity-modulated RT was performed in all patients according to the GORTEC/EORTC/RTOG guidelines. Concomitant cisplatin chemotherapy was planned at 100 mg/m^2 in days 1, 22, and 43 in all but one patient where carboplatin was chosen due to impaired renal function. Prophylactic percutaneous endoscopic gastrostomy was performed in 18 (45%) patients, and 3 (8%) patients required nasogastric feeding tube. Median follow-up was 37 months (range: 5−66).
Results: All but two patients received the planned total dose without unplanned interruption (66 Gy in 38, 64 Gy in 1, and 58 Gy in 1). According to the CTC/NCI v3.0 toxicity criteria, acute morbidity was acceptable: grade 3 mucositis in 10 (25%), grade 3 dysphagia in 9 (23%), grade 3 skin erythema in 5 (13%) patients. CT-related anemia was observed in 2 patients (grade 3 in 1, and grade 4 in 1), leukopenia in 4 patients (grade 3 in 2, and grade 4 in 2), and no grade 3 or 4 thrombocytopenia was observed. Grade 3 renal-function impairment was observed only in one patient. Median weight loss was 3.5 kg (range: 0−14.5). No treatmentrelated mortality was observed. Considering the late effects, grade 0, 1, or 2 xerostomia was observed in 9 (23%), 22 (55%), and 9 (23%) patients, respectively; grade 0, 1, and 2 edema in 25 (63%), 14 (35%), and 1 (3%) patients, respectively. Locoregional relapse was observed in 8 (20%) patients, and only 7 (18%) patients developed distant metastases. Median time to locoregional relapse was 6 months (range: 1−40). The 3-year overall, cause-specific, disease-free survival, and locoregional control rates were 65%, 69%, 64%, and 82%, respectively. Distant metastasis probability at 3 and 5 years was 19%. Univariate and multivariate analyses revealed that the only prognostic factor influencing the outcome was nodal status.
Conclusions: We conclude that reducing the overall treatment time using accelerated PORT/CT by weekly concomitant boost (6 fractions per week) combined to concomitant cisplatin chemotherapy is easily feasible with good locoregional and distant metastases control for patients operated with curative intent for LAHNC. Acute and late RT/CT-related morbidity is acceptable.

5503 ORAL

The predictive value of tumour thickness for cervical metastasis in squamous cell carcinoma of oral cavity: a meta-analysis of reported studies

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Background: Cervical metastasis greatly impacts on survival in patients with carcinoma (SCC) of the oral cavity (OC). The significant occult nodal metastasis rate warrants consideration to elective neck treatment but controversy exists as to what patient groups will benefit from such interventions. In previous studies, tumor thickness (TT) appeared a strong predictor for nodal metastasis but no consensus exists on the optimal TT cutpoint (TTcp) for a clinical relevant risk of nodal involvement. To address this question, we conducted a meta-analysis.
Methods: All articles relating to TT and nodal involvement in OC were identified through searching OVID MEDLINE (1966−4th week of 2007) and EMBASE entries. Articles were also obtained by cross-reference from citations in relevant articles. Inclusion criteria comprised: SCC of OC; any T and N categories at inception; primary surgery only; a description of the true nodal status as either node Positive or Negative for specific ranges of TT. True nodal status was assessed by either pathologic positivity on immediate neck dissection (ND) or cases without ND where neck recurrence was identified after FU $\geqslant$ 2 years. Due to inconsistency in the upper boundary of each individual study, we calculated nodal detection proportions and 95% confidence interval (CI) (Clopper-Pearson method) according to an upper level for each TT category: <3 mm, <4 mm, <5 mm and <6 mm from pooled data. Differences between TTcp were tested using Logistic Regression with Generalized Estimating Equations.
Results: Two independent reviewers selected 16 eligible studies from 72 potential studies yielding a pooled total of 1136 patients for this study. The disease subsites were 46% oral tongue, 16% buccal mucosa, 12% floor of mouth and 22% lower lip. There are 4 studies TTcp set at 3 mm, 9 at 4 mm, 6 at 5 mm and 4 at 6 mm (4 studies had 2 TTcp, 1 study had 4 TTcp). For the overall group, the proportion of subsequent node detection was 5.3% (95% CI: 2.0−11.2), 4.5% (2.6−7.2), 16.6% (11.5−22.8), and 13.0% (9.7−16.9) for TT <3 mm, <4 mm, <5 mm and <6 mm respectively. The proportion of subsequent node detection for TT < 5 mm category increased significantly compared to TT < 4 mm category ($p = 0.05$).
Conclusions: When the TTcp of OC migrates from 4 mm to 5 mm, the risk of nodal metastasis increases significantly. We propose that the optimal "cutpoint" of tumor thickness is 4 mm. For tumors thicker than 4 mm, elective treatment of the neck should be considered.

5504 ORAL

Quantification of plasma Epstein-Barr virus DNA in patients with nasopharyngeal carcinoma: results of a prospective study

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Background: Recently, quantification of plasma EBV DNA was shown to be useful for monitoring patients with nasopharyngeal carcinoma (NPC) and predicting the outcome of treatment. We designed a prospective study, to investigate the correlation between plasma EBV DNA levels and clinical status of the patients with NPC.
Methods: A total of 149 patients with NPC and healthy controls were enrolled between February 2004 and June 2006. The levels of circulating EBV DNA were measured in 3 NPC patient groups. Group A (35 patients): non-metastatic patients treated with curative intent and measurements were made at diagnosis and after treatment. Group B (82 patients): patients in remission with conventional follow-up examinations and measurements were made at follow-up. Group C (13 patients): patients with evident clinical/radiological local and/or distant relapse. Group D: 19 healthy volunteers were selected as control group.
Results: Group A: EBV DNA was detected quantitatively in plasma samples of 25 (71%) out of 35 patients at diagnosis. The median concentration of plasma EBV DNA at the time of initial diagnosis was 576 copies per milliliter (interquartile range, 41 to 15,599). The median EBV DNA concentration decreased to 0 copies per milliliter after the completion of treatment in all but four patients (3 with DM and 1 in clinical remission). Group B: During follow-up period, a quantitative increase in EBV DNA concentrations was detected in 8 (9.8%) out of 82 patients (range 0−13,731 copies/ml). The imaging of these patients revealed distant metastasis in 4, local/regional relapse in 3 and false positive in 1 patient. Group C: EBV DNA concentrations were measured quantitatively in seven (54%) of 13 patients with locoregional relapse or distant metastases. Group D: All healthy individuals have negative plasma EBV DNA.
Conclusions: This study showed that quantitative plasma EBV DNA can be detected in 71% of the NPC patients at diagnosis. The plasma EBV DNA levels were persistently undetectable or low in patients with clinical remission. These results suggest that quantitative analysis of plasma EBV DNA may be a useful clinical tool in the screening and monitoring of NPC patients.
This study is supported by Hacettepe University Scientific Research Project Unit with project number HUTF BAB 0401101007.

5505 ORAL

Large cohort dose-response analysis of parotid gland function after radiotherapy: IMRT versus conventional radiotherapy

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Background: Five years after radiotherapy, approximately half of the head-and-neck cancer patients still complain of moderate or severe xerostomia. Intensity-modulated radiotherapy (IMRT) reduces the dose to the parotid glands and thereby the number of xerostomia complications. Data regarding doses that permit preservation of parotid gland function are conflicting and originate from relatively small patient groups. Aim of this study was to compare, in a large group of patients, the parotid gland dose-response curve after IMRT with that after conventional radiotherapy (CRT).
Material and Methods: A total of 221 patients treated with primary or postoperative radiotherapy for various head-and-neck malignancies were prospectively evaluated. Of these, 64 patients were treated with IMRT and 157 with CRT (of which 49 using 3D-conformal techniques). Stimulated parotid flow rates were measured before radiotherapy and 6 weeks, 6 months and one year after radiotherapy using Lashley cups. Parotid gland dose-volume histograms were derived from CT-based treatment planning. The TD_{50} (the dose leading to a complication probability of 50%) was calculated using the normal tissue complication probability (NTCP) model proposed by Lyman and the mean dose to the parotid gland. A complication was defined as stimulated parotid flow rate <25% of the pre-radiotherapy flow rate.
Results: No difference was found between the TD_{50} value for the IMRT and conventional treatment groups (Table 1). We found rather flat dose-response curves at one year after radiotherapy (slope $m = 0.44$ for the

IMRT group and m = 0.46 for the CRT group) suggesting there is no distinct threshold dose.

Table 1. Mean dose in Gy (95% confidence interval) to the parotid gland leading to a complication probability of 50% (TD_{50}). N represents number of glands.

	6 weeks post-RT		6 months post-RT		1 year post-RT	
	Dose	N	Dose	N	Dose	N
All patients	30 (26−32)	319	34 (30−36)	254	40 (37−44)	220
CRT	32 (28−35)	222	36 (32−39)	181	40 (36−45)	168
IMRT	26 (18−29)	97	28 (20−34)	73	39 (34−48)	52

Conclusion: This large cohort dose-volume response analysis of parotid gland function shows no difference in NTCP curve between IMRT and conventional radiotherapy. One year after radiotherapy, a dose of 40 Gy results in a 50% complication probability.

5506 ORAL

Factors predicting prolonged percutaneous tube feeding in patients treated with hyperfractionated accelerated radiation therapy for advanced head and neck cancer

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Purpose/Objective: Swallowing dysfunction requiring the placement of percutaneous tubes for feeding and fluid supplementation can be prolonged for patients undergoing aggressive curative radiation for head and neck cancer (HNC). This analysis describes the incidence of and factors predicting the requirement for prolonged tube feeding in patients treated on a phase-II accelerated radiation dose escalation protocol.
Materials and Methods: Patients with stage III&VI HNC (n = 171) were enrolled in a prospective radiation dose escalation study between 1998 and 2003. Three sequential dose levels of 60, 62 and 64 Gy were delivered in 40 fractions bid over 4 weeks with non-IMRT techniques. Percutaneous tubes were inserted in 131 patients. For the first dose level, tubes were inserted as needed; prophylactic insertion was used routinely for subsequent dose levels. Tubes were removed when swallowing function had recovered enough to permit sufficient oral intake. Time between tube insertion and removal or last follow-up with the tube still in place was calculated for each patient. Kaplan-Meier rates of tube dependence were calculated for the entire group. The influence of patient (age, gender, smoking, alcohol), tumour (stage, site, recurrence), and treatment (dose, technique, field size) factors on tube dependence was examined with log rank and Cox proportional hazards models.
Results: The rate of tube dependence at 1 year post insertion was 22% for all patients. On univariate analysis, the following factors predicted for increased one year rates of tube dependence: age ($\leqslant$58 = 12% vs >58 = 32%, p < 0.0001), recurrence (no = 16% vs yes = 41%, p = 0.0058), high dose field size ($\leqslant$69 cm^2 = 12% vs >69 cm^2 = 31%, p = 0.0008), dose (60 Gy = 0% vs 62 Gy = 15% vs 64 Gy = 24%, p = 0.065), T category (T1/2 = 15% vs T3 = 22% vs T4 = 24%, p = 0.067), alcohol (no = 18% vs yes = 43%, p = 0.075) and smoking (no = 14% vs yes = 42%, p = 0.12). Gender, primary site (oropharynx vs hypopharynx vs larynx), N category and treatment technique did not have an effect. On multivariate analysis only age and relapse were significant (p = 0.0014 and p = 0.003 respectively).
Conclusions: Actuarial rates of tube dependence in HNC patients treated with this aggressive accelerated radiation regimen are significant. Age greater than 58 and the presence of recurrent disease were the strongest independent predictors of tube dependence, however other factors should be considered when informing patients of the risk of this complication.

5507 ORAL

A phase 2 study of axitinib (AG-013736; AG) in patients (pts) with advanced thyroid cancers

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Background: AG is a potent small molecule inhibitor of VEGFR 1, 2 and 3. The efficacy and safety of AG was examined in pts with advanced thyroid cancers in a single-arm, multi-center study. Increased concentrations of plasma VEGF and decreased concentrations of soluble VEGFR2 and/or VEGFR3 have been observed after treatment with VEGFR inhibitors, and the relationship between clinical response and soluble protein was also explored.
Methods: 60 pts with metastatic or unresectable locally advanced thyroid cancer refractory to, or not suitable candidates for, ^{131}iodine (^{131}I) treatment, with measurable disease received AG (starting dose 5 mg orally BID). The primary endpoint was response rate (RR) by RECIST criteria. A Simon 2-stage minimax design was used (α = 0.1; β = 0.1; null RR = 5%; alternative RR = 20%). Samples were collected at baseline and q8wks to assess pharmacological modulation of plasma VEGF, soluble VEGFR2, VEGFR3 and KIT.
Results: Median age was 59 yrs (26−84), 35 (58%) were male. Histological subtypes included papillary: 29 pts (48%); follicular: 15 pts (25%), including 11 (18%) with Hurthle cell variant; medullary: 12 pts (20%); anaplastic: 2 pts (3%), and other/unknown: 2 pts (3%). 53 pts (88%) had prior surgery, 42 (70%) had prior ^{131}I treatment, 27 (45%) had prior external beam radiation, and 9 (15%) had prior chemotherapy. Partial response by investigator was achieved in 13 pts (22%, CI: 12.1, 34.2), with 31−68% maximum tumor regression and duration of response (DOR) of 1−16 months. 30 pts (50%) have stable disease with a DOR of 4−13 months and 13−67% maximum tumor regression in 28 pts. Response assessments are ongoing. Treatment duration range is 6–670 days with 38 pts currently on study. Median PFS has not been reached with a median follow up of 273 days. The most common treatment-related adverse events were fatigue (37%), proteinuria (27%), stomatitis/mucositis (25%), diarrhea (22%), hypertension (20%) and nausea (18%). Plasma VEGF increased by approximately 2.8-fold after 3 days of AG treatment. AG therapy decreased soluble VEGFR2 and VEGFR3 by 32 and 35%, respectively compared with baseline. In contrast, a relatively modest decrease in soluble KIT of 13% was observed (although statistically significant).
Conclusions: AG has substantial anti-tumor activity in advanced thyroid cancer and demonstrated pharmacodynamic activity as a selective VEGFR inhibitor. A global pivotal trial testing AG in doxorubicin-refractory thyroid cancer is ongoing.

Poster presentations (Tue, 25 Sep, 09:00−12:00)

Head and neck cancer

5508 POSTER

Efficacy of BIBW 2992, a potent irreversible inhibitor of EGFR and HER2, in models of head and neck cancer

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Background: EGFR is highly expressed in approximately 90% of head and neck squamous cell carcinomas (HNSCC). Cetuximab, a monoclonal antibody targeting EGFR, has demonstrated clinical benefit in HNSCC patients in combination with radiotherapy (locally advanced disease). More recently, a high incidence of EGFR mutations resulting in a deletion in the extracellular domain (EGFRvIII) has been reported in HNSCC. BIBW 2992 is a potent inhibitor of both EGFR (IC50 = 0.5 nM) and HER2 (IC50 = 14 nM) receptor tyrosine kinase activity with high selectivity against a panel of more than 50 other kinases. In vivo studies in nude mice have shown excellent single-agent efficacy in xenograft models of human breast, gastric, ovarian and vulvar carcinomas. BIBW 2992 demonstrated encouraging results in phase I studies and is currently in phase II clinical trials.