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.

Materials and Methods: The present study investigates BIBW 2992 in models derived from HNSCC.
Results: In vitro, BIBW 2992 inhibited the proliferation of transfected Ba/F3 cells expressing the wild-type receptor with EC50 = 0.8 nM. Importantly, the compound showed similar potency on Ba/F3 cells expressing the EGFRvIII mutant receptor (EC50 = 0.5 nM). BIBW 2992 inhibited the proliferation of the HNSCC cell line FaDu with an EC50 of 7 nM. Cell cycle analysis by propidium iodide staining of treated cells showed a reduction of S-phase cells and a concomitant increase of G0/G1 cells at concentrations that match the EC50 values observed in the proliferation assays. In in vitro combination experiments BIBW 2992 shows at least additive activity when added to standard chemotherapeutics used in HNSCC patients (e.g. 5FU or taxanes). In vivo, potent, dose-dependent and long-lasting growth suppression and even tumor regressions were observed when mice carrying subcutaneous FaDu xenografts were treated daily p.o. with 20 mg/kg BIBW 2992. Short term treatment (3 days) of mice with BIBW 2992 before a single 20 Gy dose did not result in significant sensitization to radiotherapy. However, long term treatment with BIBW 2992 after a 20 Gy dose of radiation resulted in a tumor volume doubling time of 104 days thus slowing tumor growth by more than 3-fold. Combination of BIBW 2992 at suboptimal doses with the triple angiokinase inhibitor, BIBF 1120, resulted in improved efficacy in the FaDu model.
Conclusion: BIBW 2992 shows efficacy in human HNSCC models in vitro and in vivo. Clinical studies in this tumour type seem warranted.

5509 POSTER

Multicomponent coatings improve the biocompatibility of load-bearing implants

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Aim and Innovation: At this work was to estimate the influence of new multicomponent nanostructured coatings on the implant's osseointegration process. Titanium implants commonly used in orthopedics and dentistry integrate into host bone by a complex and coordinated process. The results of their application are completely satisfactory in many instances; however, are encountered the cases of the complications, which can be treated as the consequences of the insufficient biocompatibility of pure titanium. The signs of inflammation, thinning the skin, threat of the formation of sore and even fistulae can be seen. The danger of the similar complications development makes it necessary the search for titanium implants coatings, which would improve their biocompatibility and osseointegration. Osseointegration is a direct connection between living bone and the titanium implant at the level of the light microscope. Comparing with the previous studies new implants are studied in vivo under the conditions, when the replaced defect is located on the bone, which accomplishes motions with the large amplitude and with the large load.
Methods and Materials: of this investigation 48 rats femur model (250–300 g) were used. 3 types of implants were placed: one type had pure titanium core with TiC0.5 + 10%($Ca_{10}(PO4)_6(OH)_2$) composition coated on the surface. The average grain size is 10−40 nm. Another type had pure titanium core with TiC0.5 + CaO composition coated on the surface. The average grain size is 10−40 nm as well. The control was a pure titanium implant. An osteotomy was performed, and a 3 mm length of femur was removed. The implant was placed into the animal's tissue. Four screws fasten the implant to the femur's fragments fixing them. The animals were allowed full weight bearing without any mobility restrictions immediately postoperatively. Standard plain radiographs of the dissected bones were taken in lateral projections to ensure implant's stability. The rats were sacrificed and tissues investigated 5, 10, 15 and 30 days postoperatively.The degree of osseointegration correlates with the presence of osteocalcine, a differentiation marker of mature bone cells. The more rapidly increases osteocalcine concentration on the boundary between the bone and the implant, the more biocompatible implant appears.
Results: the effectiveness of implants considered in comparison with a control group of implants without nanostructured modification was proved by experimental models not only for stable, but also for moving with the large amplitude load-bearing implants.

5510 POSTER

Heparanase expression in the differentiation of follicular thyroid lesions: from laboratory to clinical practice

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The papillary, follicular, medullary and anaplastic variants of thyroid carcinoma can be promptly diagnosed by cytological criteria in material obtained by fine-needle aspiration (FNA) ultrasonography-guided. However, the distinction between follicular carcinoma and benign follicular adenoma needs histological demonstration of vascular or capsule invasion; therefore, they are cytologically grouped as undetermined tumors or suspect follicular neoplasm ("follicular pattern"). The aim of this study was to evaluate the immunohistochemical expression of heparanase, an endo-beta-glucoronidase, implicated in the process of tumor invasion in histological fields of thyroid follicular adenomas and carcinomas in an attempt to make a differential diagnosis of these neoplasms. Forty-nine thyroid follicular adenomas and 11 thyroid follicular carcinomas were evaluated, using the monoclonal antibody anti-heparanase by immunohistochemical reactions through the LSAB-peroxidase technique. The analysis was made by a quantitative digital computer-assisted method (Imagelab®). The immnunostaining analysis obtained showed a distinct pattern between follicular adenomas and carcinomas: while carcinomas showed positive immunostaining on neoplasic cells and negative immunostaining on coloid, adenomas showed an inverse pattern. This test presents sensibility of 91%, specificity of 86% and negative predict value of 98%. In conclusion, the association of positive heparanase on neoplasic cells and negative heparanase on coloid is a good immnuohistochemical test in the exclusion diagnosis of thyroid follicular carcinoma when compared to adenomas, with high sensibility, specificity and negative predict value.

5511 POSTER

The use of a radiophotoluminescent glass rod detector for the determination of cyberknife stereotactic radiosurgery system output factors

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Background: The Cyberknife (CK) radiosurery system can deliver single or several fractions of radiation doses to a well-defined small intracranial or extracranial target with a high precision. A radiophotoluminescent glass rod detector (GRD) system has recently become commercially available. The purpose of this study is to evaluate the possibility of the GRD as a new detector for dose measurement in small fields and high dose gradient regions. We introduce a novel method for measurement of 5 mm output factor for the CK using GRD. Although the concept of using GRD to determine output factors is not new, they have not gained measured output factor in water phantom The GRD holder is specially designed for this study to put into the water phantom for the irradiations.
Materials and Methods: In this study, the model GD-301 glass rod dosimeter (Asahi Techno Glass Corporation, Japan) and FGD-1000 automatic reader are used. The size of the model GD-301 is 1.5 mm in diameter and 8.5 mm in length. The relative output factor of CK collimators(5, 7.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 50 and 60 mm) measurements with the GRD were compared with those with a PTW 60008 diode detector, PTW 31006 pinpoint type ionization chamber and a Gafchromic film (Type MD-55). The output measured with GRD, pinpoint chamber and diode was performed at a depth of 1.5 cm in water phantom. The GRD was irradiated in a water phantom using a holder stand, which was specially designed for this study. The holder is composed of the PMMA tube with a hole for GRD at 1.5 cm from its top. The water level was set precisely to the top of the holder and the axis of the beam aligned with holder axis in a way that the radiation beams pointed down vertically.
Results: The measured relative output factors with four dosimeters shown very similar results except for three smallest collimators (5, 7.5 and 10 mm). The mean value of the output factor for GRD in the 5 mm collimator is 0.705. Each dose point of GRD is presented by an average of 5GRD readings and their one standard deviation of each dose point is within ±1.0%.The pinpoint chamber output is approximately 11% lower than the corresponding GRD values at the 5 mm collimator. Because the pinpoint chamber had a larger effective volume, this most likely contributed to these differences. The GRD is 5.2% and 4.1% lower than diode in the 7.5 mm and 5 mm collimators, respectively. It is not obvious whether the difference