Methods and Materials: Sixteen head and neck cancer patients, irradiated between September 1999 and November 2000 using a conformal parotid-sparing technique, were included in this study. Before RT and seven months after RT a salivary gland scintigraphy was performed in all patients combined with a single photon emission computed tomography (SPECT). The salivary excretion function (SEF) was measured, after stimulation, in 8-12 transversal 5 mm SPECT slices of each parotid. Loss of salivary function in these areas (dSEF%) was calculated as a proportion of the excretion function before and after RT. Because the planning CT-scan and the SPECT analysis were performed in the same treatment position, doses to areas within the parotid gland could be matched with the dysfunction of that respective area. For each patient, dose-dysfunction plots were performed and curve fitting was done.

Results: At baseline level, all but one patient had a normal salivary excretion function at the level of both parotid glands with small variation between the functionality of the different areas within the same gland. Seven months after RT, the reduction in salivary excretion function reached statistically significance for both parotids and a huge variation in functionality of the different areas within the same gland could be seen. When plotting the dysfunction of the different areas within one gland at seven months after RT against the dose these areas received, a sigmoidal function could be fit in seven (7/15) patients to the plots of both parotids and in five (5/15) patients to the plot of one parotid gland. In three (3/15) patients no dose-response curve could be fit to the plots due to a total dysfunction of all partial volumes or an absence of difference in dose between the volumes. In nine (9/15) patients a large variety of functional responses could be obtained at low irradiation doses (10-15 Gy), ranging from an improvement of function to a total loss.

Conclusion: Salivary SPECT is a useful tool for the evaluation of functional loss after RT of different areas within the parotid gland. While these areas are acting as functional sub-units under normal conditions, their dysfunction after RT does not seem to be only the result of the absolute dose these volumes received but also of the mean dose to the entire parotid gland and the dose to the surrounding areas.

470 POSTER

Severe radiation-induced bowel complications are not uncommon in patients with uterine cervix cancer

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Background: To evaluate the factors of severe (Grade 3-4) bowel complications after external irradiation and high dose-rate intracavitary (HDR-IC) brachytherapy among patients with cervical cancer.

Materials and Methods: We reviewed 298 patients of stage IB-IVA cervical cancer managed by curative-intent radiotherapy from May 1993 through December 1997. External irradiation to whole pelvis (34.2-50 Gy/ 19-27 fractions) was delivered to all patients initially. Two hundred and three patients received additional bilateral parametrial boost (3.6-18 Gy/ 2-10 fractions) with 4-cm midline shielding. HDR-IC brachytherapy, 16-24 Gy/ 5 fractions to Point A, was given after external irradiation. External parametrial dose < 50 Gy, 50-54 Gy and > 54 Gy were categorized as low parametrial dose (LPMD), intermediate parametrial dose (IPMD) and high parametrial dose (HPMD) group, respectively. Cumulative rectal biologic effective dose (CRBED) < 85 Gy, 85-105 Gy and > 105 Gy were categorized as low cumulative rectal biologic effective dose (LCRBED), intermediate cumulative rectal biologic effective dose (ICRBED) and high cumulative rectal biologic effective dose (HCRBED) group, respectively. The actuarial rate of bowel complications was compared among groups. We used Cox regression for multivariate analysis of bowel complications.

Results: Grade 3-4 bowel complication rates were 16%. The rates were 7%, 13%, and 34% in the LPMD, IPMD, and HPMD group (p=0.0001), respectively. The rates were 5%, 11%, and 28% in the LCRBED, ICRBED, and HCRBED group (p=0.0002), respectively. In multivariate analysis of Grade 3-4 radiation-induced bowel complications, CRBED (p=0.0010) and external parametrial dose (p=0.0007) were independent factors.

Conclusions: Radiation-induced severe bowel complications are depended on external parametrial dose and CRBED. We do not suggest external parametrial dose > 54 Gy and CRBED > 105 Gy for treatment of cervical cancer due to relatively high incidence of severe bowel complications.

471 POSTER

Radiation-induced changes in the cytoskeleton of human endothelial cells in relation to endothelial monolayer permeability.

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Treatment of solid tumours by radiotherapy damages the tumour cells as well as the microvasculature of the tumour and surrounding normal tissues. An increase in vascular permeability is a well known effect of radiation, which contributes toward changes in the interstitial space that lead to reduction of parenchymal cell function, necrosis and fibrosis. A response to radiation by normal tissue endothelium is thought to be a major limitation for its use in cancer treatment.

The aims of the present study were to investigate the early effects of radiation on the cytoskeleton of cultured endothelial cells and relate these to changes in endothelial monolayer permeability.

Human dermal microvascular endothelial cells (DMEC) were irradiated using a Pantak X-ray machine. Using immunofluorescence techniques, DMEC were found to respond to various doses of radiation (0.5 - 20 Gy) by a rapid (within minutes) increase in actin reorganization into stress fibers, accompanied by changes in the distribution of the adherens junction protein, VE-cadherin. Increased endothelial stress fiber formation, cell contraction and redistribution of junctional proteins can lead to intercellular gap formation and changes in monolayer permeability. Therefore, changes in permeability were quantified by monitoring the passage of fluorescently-labelled dextran through DMEC monolayers grown on microporous filters. Radiation was found to induce a significant increase in DMEC permeability suggesting that the changes in the actin cytoskeleton and distribution of cadherins were associated with increased monolayer permeability. Activation of the GTPase Rho and its associated Rho kinase have been recognised as key regulators of the actin cytoskeleton, intercellular junction integrity and permeability. Analysis of the mechanisms involved in irradiation-induced actin reorganisation, re-distribution of VE-cadherin and increased permeability revealed that these effects of radiation were dependent on activation of Rho kinase, since they were blocked by the highly specific Rho kinase inhibitor Y-27632. Simvastatin, a 3-hydroxy-3-methylglutaryl CoA reductase inhibitor used clinically for the treatment of hypercholesterolemia, is known to inactivate Rho by inhibiting its geranylgeranylation. Simvastatin was found to inhibit the radiation mediated changes in actin and junctional proteins as well as increased permeability suggesting the involvement of Rho.

These data provide an insight into possible mechanisms involved in radiation-induced changes in vascular permeability. Further investigations are needed in order to elucidate whether compounds such as Y-27632 and simvastatin may be useful in counteracting some of the side effects of radiation *in vivo*.

472 POSTER

Efficacy and morbidity of linear accelerator radiosurgery for cerebral arteriovenous malformations: a comparison with the natural history

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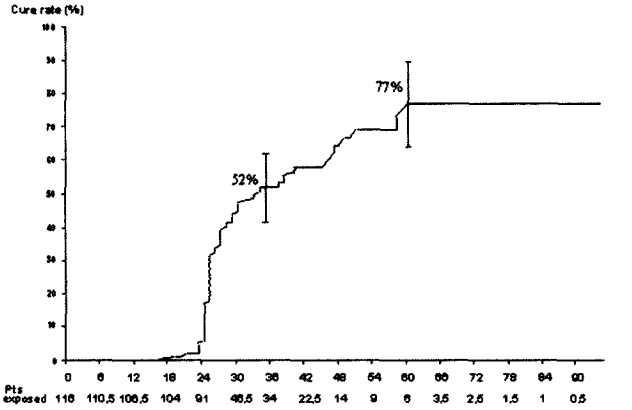
Background: To report the results of arc-therapy radiosurgery in terms of efficacy. To compare the adverse-effects rate with the one expected from the natural history.

Material and methods: At the University Hospital of Nancy, 217 patients have been treated for cerebral ArterioVenous Malformation (AVM) by linear accelerator radiosurgery since 1992. We report here the results of a retrospective study of the 118 first patients (55 men, 63 women) treated between 01/07/92 and 30/06/98. The mean follow-up was 46 months (5-105). The mean age was 35 years (13-65). AVMs had poor prognosis features at initial presentation: existence of previous therapeutic failures (85%), high Spetzler-Martin grade (67% of grade III or higher), large size (57% > 14cc) and a high rate of initial hemorrhage (54%). Patients had already been treated by previous embolizations with a mean number of 4 procedures (1-11) in 84% of patients (99/118); 79% by embolizations alone (93/118) and 5% by partial microsurgery and embolization (6/118).

Radiosurgery involved the irradiation of 92% of (109/118) of two targets in 7% of patients (8/118) and of three targets in less than 1% of patients (1/118). All targets were irradiated with a single isocenter. The mean volume of the targets was 7.4cc (0.3-28.3). The mean minimal dose was 17.4 Gy (10-25) and the maximal dose 24.5 Gy (17-36).

Results: The crude and 5-year actuarial rates of cure were respectively 54% (60/112) and 77%. The only independent prognostic factor of cure was volume of the AVM with a cut-off at 7cc (crude cure rate of 67% for <7cc vs. 35% for > or =7cc; p=0.001). No patient died. Permanent complications occurred in 1.7% of patients (2/116) due to radionecrosis or lesion that evolved towards radionecrosis (one hemiparesia and one hemiparesthesia with aphasia). Transient complications occurred in 5% of patients (6/116) (2 cases of hemiparesia, one confusion, one headache, 2 cases of worsened epilepsy). A hemorrhage after radiosurgery occurred in 6% of patients (7/116) with a mean time of 32 months (5-81). Salvage treatment was safe and possible in 19% of uncured patients (10/52) either by use of microsurgery, embolization, a combination of both or a new radiosurgical procedure. Salvage treatment achieved cure in 40% of patients (4/10). All the patients who achieved either a cure (54%: 60/112) or an occlusion of more than 95% of the initial volume of the AVM without cure (20%: 23/112) were free of subsequent hemorrhage. The annual risk of hemorrhage was 1.7% (0.7%-3.4%).

Actuarial rate of Cure of Arterio-Venous Malformation by radiosurgery (Kaplan-Meier)



Conclusion: Our study confirms that radiosurgery is an effective treatment (5-year actuarial cure rate of 77%) of AVM with a low rate of complications. The rate of hemorrhage after radiosurgery is low, nil after cure or with a volume reduction of more than 95%. The rate of adverse-events is comparable to the one expected from the natural history of untreated AVMs.

473 POSTER

The initial clinical experience utilizing an implantable dosimeter for measuring true in vivo radiation dose during external beam radiotherapy

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Purpose: A reliable *in vivo* method for measuring the dose of radiation delivered at depth does not exist. An implantable telemetric device has been developed to monitor, in real time, the dose delivered at the target site. The final results of the pre-clinical study verified the safety of the implantable device, the lack of adverse events and the ability to measure delivered dose. The purpose of this report is to outline the clinical trial and report on the initial results of the clinical study

Methods and Materials: The implantable device is a product of Sicel Technologies Inc. The pilot study will have 10 patients, with unresectable malignant disease, from any site except brain. The primary end points of this study are to a) assess the safety associated with implantation and movement of the device (adverse events) b) to compare the *in vivo* measured dose with the calculated dose. The device measures 22.0 x 2.5mm and was designed as a permanent implant. As of this submission, 6 patients have been entered onto study. The sites include lung (2), rectal (1), prostate (2) and sarcoma of extremity (1). Following implantation of the dosimeters, standard radiotherapeutic methods were instituted, including simulation and treatment-planning CT scans. A dose point calculation for the predicted dose was determined at the location of the dosimeter end of the device. After the initiation of radiation therapy, the *in vivo* radiation dose was measured daily following each treatment session, and treatment planning CT scans was repeated at 2 and 4 weeks to determine movement of the dosimeters.

Results: The first two patients implanted have completed their planned radiation therapy as of this submission. The remaining 4 patients are in various phases of treatment. The results of the remaining patients will be presented utilizing the same format. There have been no adverse events to date. The results from repeat CT scans did not reveal any significant movement. In the first patient, the average measured dose at the normal tissue was 4% greater than the computed dose during treatment with AP-PA fields, whereas the average measured dose at the gross tumor volume (GTV) was 8.9% less than computed when treating with simple oblique fields. In the second patient, the average percent difference between the measured and computed dose was less than observed with the first patient but was increased by 10% for the final boost.

Conclusions: This report represents the results of the initial pilot study on a permanently implantable *in vivo* dosimeter. The initial results indicate that the device is safe and without associated adverse reaction. There are a number of possible explanations for the variance in radiation dose (e.g. tumor or organ movement), however regardless of the cause the dose recorded by the *in vivo* dosimeter is considered the result of the sum of all the possibilities.

474 POSTER

Plasma Osteopontin (OPN) predicts hypoxia and response to the hypoxic sensitiser Nimorazole in radiotherapy of head and neck cancer. Results from the randomized DAHANCA 5 trial.

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Background: OPN has recently been found to correlate with VHL expression in head and neck cancer, and high level of OPN is found to be associated with tumour hypoxia and expression of HIF-±. The DAHANCA 5 study evaluated the effect of the hypoxic radiosensitizer nimorazole (NIM) and found it to significantly improve the outcome of radiotherapy in supraglottic and pharynx tumours. It is, however, unclear whether all patients may benefit from such hypoxic modification and the aim of the present study was to evaluate in a randomized setting whether OPN had prognostic influence on the outcome as a function of treatment with NIM, and if so, to evaluate whether plasma OPN level was predictive of the response to the hypoxic sensitizer.

Materials and methods: Stored plasma samples from 326 of the 414 originally included patients were available for analysis. Plasma OPN was measured by ELISA (Assay Designs, Inc) and data was evaluated by 5-year actuarial univariate and Cox multivariate analyses. All procedures were as previously described (Rad. Oncol. 46:135-56, 1998).

Results: The 326 analyzed patients were representative of all 414 in the trial and did overall show a significant difference in loco-regional control in favour of NIM with 5-year values of 55% vs. 44%, p=0.05. Plasma OPN level ranges from 12 to 1659 ng/ml. The distribution of OPN values (divided into tertiles) was the same in both treatment arms, and with slightly higher values in N+ patients. Otherwise there was no significant relationship with classical prognostic parameters. Patients with high OPN level had a significantly poorer loco-regional control and survival, but detailed analysis showed that this was only observed in the placebo treated patients, whereas NIM treated showed no relationship between OPN level and outcome. Analyzing the odds ratio for the tertiles as a function of NIM treatment showed an odds ratio for patients with low OPN level of 1.0 (0.5-2.2, 95% cf.l.) and for intermediate of 0.9 (0.4-1.8), whereas for high OPN levels there was a significantly better outcome in the NIM treated patients 0.3 (0.1-0.6), p<0.01. Actuarial analysis confirmed that there was a significant benefit in 5-year loco-regional control (52% vs. 27%), p=0.01and cancer specific survival (45% vs. 25%), p<0.05, if NIM was given to patients with high OPN level. This was confirmed by multivariate analysis which showed no influence of OPN level in NIM treated patients, whereas high OPN level was highly significant for poor outcome in placebo treated patients.

Conclusion: Plasma OPN is an easily obtainable marker and high level is associated with poor prognosis after radiotherapy to head and neck cancer patients. This could be reversed by given such patients with NIM together with radiotherapy. The study is thus indicative of OPN as a predictor for clinical relevant hypoxia and may predict the patients who may benefit from hypoxic modification. OPN measurements should be included in clinical trials evaluating hypoxic modification in order to confirm this hypothesis.

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