images reviewed by one experienced radiologist. Median time of onset was 44 months (range 6 - 197). All patients had pain as the first symptom. The only independent predictive factor for developing osteoradionecrosis was pre-existent osteoporosis. Other risk factors, including higher age, postmenopausal status or steroide treatment, are all related to osteoporosis. We didn't find any significant treatment-related predictive factor for pelvic osteoradionecrosis.

Conclusion: Patients with osteoporosis are at highest risk for developing osteoradionecrotic fractures after pelvic radiotherapy. More studies are needed to find out other endogenous predictive factors (e.g.TGF-beta).

731 POSTER

Time-dose-response relationships in patients with head and neck squamous cell carcinomas treated by surgery and postoperative radiotherapy

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Purpose: To define the influence of the dose and time on the response to treatment in postoperatively irradiated head and neck cancer patients and to establish a good prediction of failure.

Methods and Materials: From January 1985 to December 1995, 214 patients with histologically proven head and neck squamous cell carcinomas were irradiated after radical surgery or single tumour resection according to surgical and histopathologic findings. The total doses given ranged between 50–75 Gy to the primary bed tumour and between 42–56 Gy to the neck with fraction sizes of 1.7–2 Gy/day. The median length of the time interval between surgery and radiotherapy, time of irradiation and total treatment time was 81 days, 59 days and 139 days, respectively. The end-point analysed was the local-regional tumour control rate at the primary tumour bed and neck for 5 years from the beginning of radiotherapy. Univariate and multivariate analyses were used to determine predictors of failure from among the following studied variables: i) clinical stage (T/N) of the patients; ii) tumour grade; iii) neck surgery; iv) tumour margins; v) histological tumour nodal extension; vi) chemotherapy; vii) normalised total dose; viii) time interval between surgery and radiotherapy; ix) time of irradiation; and x) total treatment time.

Results: The actuarial 5 years tumour control rate for the entire group was 72%, and 92% of the patients who achieved local control are currently alive without disease. Tumour control was inversely related to T stage (83% for T_2 vs. 57% for T_4) and the probability of local control within each stage was dependent on the N status ($\geq$71% for T_3-T_4/N_0 vs. 31–44% for T_3-T_4/N_1-N_3). Histological N status and tumour margins, but not tumour grade, impacted significantly on tumour control. When local control was analysed as a function of the dose to the primary, a nonsignificant negative dose-response relationship was found. The total treatment time was a significant prognostic factor and the time interval between surgery and irradiation proved to be an independent predictor of failure.

732 POSTER

Improving the quality of care in a rural radiation oncology center through use of telemedicine

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Purpose: In 1998, in a rural region of the United States, a telemedicine system was used to link a community radiation oncology center with an academic center of medical excellence in an effort to improve care.

Methods and Materials: A tele-medicine system was installed in both centers to allow remote consultation and review of treatment related radiographs. A 3-D compatible treatment planning system and practice management software allowed on-line review of treatment plans and data. A comprehensive quality assurance program was instituted. In December of 2000, utilization of the tele-radiography system and the trend of quality assurance indicators were assessed.

Results: The teleradiography system was used for peer review of all cases. This system was also used for sub-specialty consultation in the treatment of uncommon malignancies. The integrated treatment planning system allowed the simulation and treatment planning for complicated cases to be performed in the academic center and then the treatment was delivered in the community center. Quality assurance parameters showed a positive trend. Treatment accuracy, as measured by the deviation between the central axis simulation and portal films, was assessed. In 1998, 96% of port films (2,828 of 2,949) were within 0.5 cm and 1% (23 of 2,949) were greater than 1.0 cm. In 2000, 97% (4,111 of 4,245) were within 0.5 cm and 0% (17 of 4,245) were greater than 1.0 cm. Discrepancies between prescribed and treated field parameters improved significantly, from 0.9% (84 events/9,632 patient visits) to 0.3% (25 events/10,162 patient visits) between 1998 and 2000. Physicist chart reviews revealed deviations of 5-10% from prescribed parameters in 1.1% (15 of 1,375) and >10% in 1.2% (16 of 1,375) of charts reviewed in 1998 and deviations of 5-10% in 0.0% (0 of 2,096) and >10% 0.7% (15 of 2,096) in 2000.

Conclusions: Objectively, quality assurance indicators revealed a modest, but measurable, improvement following incorporation of the rural center into a regional oncology network. Subjectively, the teleconferencing system was useful in obtaining expert advice in treating less common malignancies as well providing on-going opportunities for continuing education.

733 POSTER

The concentration-dependency of the radiosensitising effect of gemcitabine and the influence of the rescue agent amifostine in vitro

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Gemcitabine (dFdC) is an active antitumour agent with radiosensitising properties. Since the combined use of dFdC and radiotherapy (RT) also results in an increased toxicity, there is a need for optimisation of this combined approach. Cytoprotective agents might be utilised to reduce these toxic effects. In that respect, amifostine (ami) is one of the most promising cytoprotectors that in vivo selectively protects normal tissues against radiation- or chemotherapy-induced toxicities. We studied the concentration-dependency of the radiosensitising effect of dFdC and the combination of dFdC/RT with ami in various cell lines.

H292 and A549, two lung cancer cell lines, ECV304, a bladder cancer cell line and CAL-27, a carcinoma cell line of the tongue were used in this study. The cells were treated with 0, 1, 2, 4, 6 and 8 nM dFdC for 24 hrs prior to RT. Ami (3.5 mM) and alkaline phosphatase (7.5 U/ml) were added 30 min prior to RT. Cells were irradiated at room temperature by 60Co over a dose range of 0-8 Gy. Cell survival was determined 7 days after RT by the sulforhodamine B test. ID50, radiation dose resulting in 50% cell kill was calculated from the survival curves, fitted according to the linear-quadratic model: survival=exp(-aD-bD2). The radiosensitising effect is reflected by the dose enhancement factor (DEF): ID50(-dFdC)/ID50(+dFdC). The protection factor (PF) was calculated by ID50(+ami)/ID50(-ami).

For ECV304 cells the DEFs varied from 1.39 to 2.98 after treatment with 1 to 6 nM dFdC. H292, A549 and CAL-27 seemed to be less sensitive for the radiosensitising effect of dFdC, with DEFs ranging from 1.05 to 2.67, 1.02 to 2.52 and 1.06 to 2.52 for 1 to 8 nM dFdC, resp. H292, A549 and CAL-27 cells were also less sensitive for the cytotoxic effect of dFdC: IC50 values (conc. causing 50% cell kill) were 8.0, 9.0 and 8.9 nM in H292, A549 and CAL-27 cells, respectively, while in ECV304 the IC50 was 3.1 nM. In combination with dFdC/RT ami clearly showed a protective effect. In H292 cells the PF of ami after treatment with 4 nM dFdC/RT was 1.64 and with 8 nM dFdC the PF was 1.86.

In conclusion, we observed a concentration- and cell line-dependent radiosensitising effect of dFdC in vitro, which seemed to correlate with the sensitivity of the cell line for the cytotoxic effect of dFdC. Ami clearly showed protective effects. Since these protective effects seem to occur selectively in normal tissues ami should be used to further optimise dFdC/RT combinations.

734 POSTER

Loss of alkaline phosphatase expression in breast carcinoma: Implications in the amifostine selective cytoprotection

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Introduction: Amifostine (WR-2721) is an importance cytoprotective agent widely used in clinical oncology to protect normal tissues against radiation and chemotherapy. This is an inactive compound that becomes dephosphorylated to an active thiol (WR-1065) by the enzyme alkaline phosphatase (AF), abundantly found in the normal endothelium. Although a direct evidence is missing, it is believed that amifostine selectively protects normal tissues and not the tumors, as AF is down-regulated in the tumoral vasculature.

Materials and Methods: In the present study we sought a direct evidence of such an AF down-regulation in breast cancer by studying immunohistochemically the expression of AF (Z0271 PolyAb against the intestinal type of AF) in normal an cancerous breast. Differences in the AF activity between normal and tumoral vasculature was assessed by comparatively counting the microvessel density (MVD) of CD31 and AF positive vessels.

Results: In the normal breast, the glandular epithelium, the fibroblasts and the vessels expressed persistently a strong mixed cytoplasmic/nuclear reactivity for AF. The mean MVD using the panendothelial cell marker CD31 was 2410. The MVD of AF positive vessels was 23+-9, which was not different, showing that all vessels in the normal breast express AF. The invasive cancer cells almost never expressed nuclear AF. Strong cytoplasmic AF expression was noted in 11/41 (26%) cases examined. The stromal fibroblasts around the tumor invading front and within the tumor were persistently negative. In situ carcinoma lesions showed invariably loss of nuclear expression of AF. Tumoural vessels were only occasionally stained for AF. The median percentage of vessels expressing AF in the invading front was 19% (range 0-46%) and in inner areas 6% (range 0-28%).

Conclusions: Taking into account the striking difference of AF expression between normal and cancerous breast, as well as the fact that stromal fibroblasts consist the largest component of both the normal breast and cancer tissue, we suggest that stromal AF activity may be an important factor that regulates the selective dephosphorylation of amifostine to the active cytoprotector WR-1065 in normal and not in cancerous breast tissues.

735 POSTER

Does time of day of radiation therapy affect treatment outcome? The circadian/melatonin hypothesis

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Background: The pineal hormone melatonin has been suggested to be an effective anti-cancer therapeutic agent, and deficiency in melatonin has been implicated as a possible etiologic factor in the development of certain cancers. One small randomized trial suggests that melatonin is effective in treating lung cancer. Other studies demonstrate that melatonin is effective at treating human breast cancer cell lines in vitro. Melatonin levels follow a circadian rhythm in humans, with plasma levels remaining low throughout the day, rising slowly in the late afternoon and then rapidly increasing after darkness. We sought to determine if patients with breast and lung cancer treated later in the day - when melatonin levels should be higher - had improved outcomes.

Methods and materials: Information on time of day of treatment was available for 185 (106 breast, 79 lung) patients treated from 1997-1999. All patients had non-metastatic disease at the time of treatment. We used a cutoff time of 4 PM EST to split patients into an Early Group (EG), and Late Group (LG). We chose this cutoff to represent a point at which the patients' serum melatonin concentrations would be expected to begin to rise.

Results: Mean FU was 29 months and 15 months for patients with breast and lung cancer, respectively. For patients with breast cancer, 87 patients were in EG, 19 in LG. Overall Survival (OS) at 2 years was 97.5% for EG, 100% for LG. Disease-Free Survival at 2 years was 86.5% for EG, 86.2% for LG. These differences were not significant. Among patients with lung cancer, 67 patients were in EG and 17 in LG. For these patients, OS was 36.4% for EG, 47.1% for LG. Median OS was 12.1 months for EG, 10.7 months for LG. These differences were not significant. 2 year DFS was 25.5% for EG, 41.3% for LG (p=0.186). Median DFS was 8.4 months for EG and 14.8 months for LG.

Conclusion: In this study, time of day of treatment did not affect treatment outcome. There was a slight trend toward improved DFS in patients with lung cancer but this did not reach statistical significance. These data therefore do not support the melatonin/circadian hypothesis. However, this study had a small number of patients, and a study with more patients and longer follow-up would be more powerful to detect subtle differences. Furthermore, the times at which these patients were treated may not have been late enough for melatonin concentrations to reach effective levels.

736 POSTER

Are dose volume histograms a valuable tool in predicting clinically significant pneumonitis using conformal radiotherapy in locally advanced NSCLC ?

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Purpose: The predictive value of cumulative and frequential dose volume histograms of planning target volume, boost, lung and spinal cord in 50 cases of locally advanced NSCLC St. IIIA/B was analysed regarding the incidence of clinical relevant pneumonitis grade II in correlation with V20 and Veff.

Methods: Between 05/99 until 01/01 50 patients with locally advanced non small lung cancer were irradiated using 3 D conformal technics. Evaluation of 3 D treatment planes was done using dose volume histograms. In all patients V20 an Veff were calculated and groups of patients with planning target volumes for macroscopic tumor lesser than 300 ccm and groups with volumes larger than 300 ccm were randomized. The post treatment incidence of pneumonitis grade II was compared with the estimated risk factors.

Results: V20 as well as Veff were not helpful regarding the predictive value of clinically relevant pneumonitis grade II. This complication had an incidence of 20% in our patients. Even 'optimal' planning target volumes of lesser than 300 ccm did not guarantee a good clinical tolerance of 3 D - planned irradiation. Frequential dose volume histograms can be regarded as a more differentiated tool but did not increase predictability of pneumonitis grad II.

Conclusion: The predictive value of dose volume histograms in 3 D treatment planning in locally advanced non small lung cancers is of somewhat limited value regarding clinically relevant pneumonitis grade II.

737 POSTER

Hypothalamic-pituitary dysfunction following external cranial irradiation

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Purpose: Deficiency of one or more anterior pituitary hormones may follow treatment with external radiation when the hypothalamic-pituitary axis falls in the fields of radiation. The aim of this research was to study the remote effect of external cranial irradiation on the function of the hypothalamic-pituitary axis after 2 years of follow up.

Patients and methods: Twenty eight patients, 12 children with a mean age of 6.92V2.78 years, and 16 adults with a mean age of 36.56V13.38 years were included in the study. The radiation dose received ranged from 28 to 50 Gy in children and 45 to 60 in adults. Serum concentration of GH was measured with insulin, basal serum estimation of thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone were estimated before and after irradiation.

Results: Eight patients in the pediatric group (66%) and 2 patients in the adult group had GH deficiency. Fifty percent of the pediatric group and 6.25% of the adult group had low serum TSH. Three patients in the pediatric group had ACTH deficiency. Twenty five percent of the pediatric group and 6.25% of the adult group had low serum LH/FSH. Four patients in both groups had elevated PRL. Testosterone level was low in three patients in the pediatric group, and one patient in the adult group. There were significant negative correlation between serum peak GH, ACTH, LH/FSH, testosterone and dose of irradiation.

Conclusion: patients exposed to high-dose radiotherapy (>35 Gy) to the hypothalamic-pituitary axis, a variety of endocrine abnormalities may occur, including deficiencies of GH, TSH, ACTH and LH/FSH as well as hypersecretion of prolactin.