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 24±10. 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.

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735   POSTER

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

B. Quaranta, R. Clough, L. Marks. *Duke University Medical Center, Department of Radiation Oncology, Durham, NC, USA*

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.

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736   POSTER

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

H. Paukisch[1], T. Weihrich[1], U. Ruhnow[1], W.R. Guschall[2], I. Dittrich[2], J. Bahnsen[1]. *[1] Johanniter Krankenhaus, Clinic for Radiation Oncology, Stendal, Germany; [2] Lungenklinik Lostau, Pneumonology II, Lostau, Germany*

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.

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737   POSTER

Hypothalamic-pituitary dysfunction following external cranial irradiation

A. ElGhandour[1], A. Abd ElAziz[2], M. ElBordini[3]. *[1] Faculty of Medicine, Internal Medicine/Hematology Unit, Alexandria, Egypt; [2] Faculty of Medicine, Clinical Oncology, Alexandria, Egypt; [3] Faculty of Medicine, Clinical Pathology, Alexandria, Egypt*

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.