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## MORPHOLOGICAL AND FUNCTIONAL STUDIES OF THE NASAL RESPIRATORY MUCOSA AFTER RADIATION THERAPY

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**Purpose:** Evaluation of radiation damage to the normal nasal respiratory mucosa by micro and ultramicroscopic studies and assessment of mucociliary clearance with saccharine test.

**Methods:** Before, at the end, and 6-24 months after radiotherapy (RT), transnasal biopsies were performed in the posterior aspect of the inferior turbinate in 6 patients (pts), 4 males and 2 females, aged 55-73 affected by pharyngeal squamous cell carcinomas. The area of the biopsy was not involved by the tumor but was included in the planning target volume (PTV) for RT. The total dose ranged from 69.0 to 75.9 Gy. Four pts were treated QID 2Gy/fx and 2 pts BID 1.15 Gy/fx 5 days/week. The biopsied specimens were fixed in NaCl 0.9% and glutaraldehyde 2.5%, dehydrated in alcohol and included in resin. Two millimeter slices were obtained by ultramicrotome Reichert Supernova (LW 970201) and observed with optic microscope. Eighty nanometer slices were stained with uranyl acetate and lead citrate and observed with electronic microscope.

**Results:** At the end of RT, we observed structural changes in the epithelium with decreased number of cells. In the chorion, rarefaction of blood vessels and glands with interstitial sclerosis was evident. The last biopsy showed reconstruction of the normal mucosal pattern with neovascularization and reduction of glands. These findings were in agreement with the saccharine functional test. Further observations concerning ultramicroscopic data will be presented.

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## THE INFLUENCE OF DOSE PER FRACTION ON THE PATHOGENESIS OF RADIATION NEPHROPATHY

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**PURPOSE:** The aim of this study was to determine whether there were different target cells responsible for radiation-induced nephropathy after low dose and high dose per fraction treatment and whether the capacity for recovery of damage was influenced by the dose per fraction.

**METHODS AND MATERIALS:** Both kidneys of male Wistar rats were irradiated with either 10 Gy single dose or 26 Gy with 2 Gy per fraction. Serum BUN, creatinine and blood hematocrit levels were assessed prior to radiotherapy and at intervals of 8 w. thereafter. Two animals were killed at 4, 8, 16 w. and 3 animals at 24 w. from each dose group and both kidneys of each animal were examined by electron microscopy.

**RESULTS:** In both dose groups, a significant increase in BUN and creatinine levels together with a decrease in hematocrit level was observed at 16 w. and this was followed by an apparent improvement at 24 w. There was no statistical difference in these responses between the two dose groups. The morphological changes in both dose groups were essentially similar, however they differed in severity. At 4 w. after irradiation glomerular and proximal tubular injury were observed in both groups. A marked increase of glomerular and tubular injury in the 10 Gy dose group, without any apparent progression in 26 Gy dose group, was detected at 8 w. By 16 w. a noticeable improvement in both tubular and glomerular lesions, especially in 10 Gy dose group was observed. No apparent difference from 16 w. of evaluation was found at 24 w. assessment.

**CONCLUSIONS:** These findings showed that the morphological changes observed with low doses are the same as with high doses of radiation but differ in degree and both glomerular and tubular changes are visible at the same periods of time. There is some recovery in kidney after irradiation, but the extent of recovery process is somewhat limited.

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## SILICONE TISSUE-EXPANDER PROSTHESIS (STEP) TO PROTECT THE SMALL BOWEL DURING RADIATION THERAPY FOR UTERINE MALIGNANCIES

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**Purpose:** RT-induced small bowel injury is a dose-limiting factor in gynecological cancers. Therefore, a STEP connected with a subcutaneously located self-sealing valve system was introduced surgically to push small bowel outside the treatment volume.

**Methods:** Between 1990 and 1995, 41 patients with a diagnosis of cervical (n = 35) and endometrial (n = 6) carcinoma (n = 39) or sarcoma (n = 2) were treated either with curative (n = 29) or postoperative (n = 12) RT after undergoing treatment planning simulation with the use of small bowel oral contrast medium. All patients underwent surgical placement of a temporary STEP prior to RT. Median age was 48 (25-70) years. Two patients with local relapse and 39 with new diagnosis were treated. According to the FIGO classification, there were 13 stage I, 18 stage II, 6 stage III, and 4 stage IV patients. All patients received external pelvic (n = 39) or pelvic and paraaortic (n = 2) RT with a median total dose of 59.4 (45-70.4) Gy using a median dose/fr. of 2 (1.6-3.2) Gy. Intracavitary brachytherapy was given in 38 patients with a median dose of 30 (10-45) Gy. Median AP/PA field surface was 270 (164-879) cm<sup>2</sup>; median lateral opposed field surface was 204 (159-318) cm<sup>2</sup>. Median measured small bowel surface was 6 (0-107) cm<sup>2</sup> in the AP/PA fields, and 0 (0-20) cm<sup>2</sup> in the lateral fields.

**Results:** As of January 1998, the 5-year overall and DFS was 46% and 44%, respectively. Toxicities were graded according to RTOG. During external RT there were 27 patients with G0, 9 with G1, and 5 with G2 gastrointestinal toxicity. During brachytherapy, the same toxicity was G0 in 35 patients, and G1 in 6. At the end of the treatment, only 5 patients had G1 gastrointestinal toxicity. No gastrointestinal toxicity was recorded at 3 and 6 months following treatment. Only 3 patients developed major complications requiring surgery: 2 (one small bowel obstruction and one ileus with abscess) related to STEP and one related to RT at 32 Gy (mechanical ileus) resulting with surgical correction, and application of a STEP to complete her treatment.

**Conclusions:** Placement of a silicone tissue-expander prosthesis is correlated with very low rates of gastrointestinal toxicity due to major reductions of small bowel quantity within the radiation volume without any major surgical toxicity related to its placement.

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## LONG-TERM CARDIAC MORTALITY FOLLOWING RADIATION THERAPY FOR HODGKIN'S DISEASE: ANALYSIS WITH THE RELATIV SERIALITY MODEL

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**Purpose:** a) To assess the increased risk of Ischemic heart disease (IHD) death in the patients treated for Hodgkin's disease with radiation therapy as primary treatment at a single institution. b) To quantify the dose response of IHD using the relative seriality model of normal tissue complication probability (NTCP) and individual clinical data.

**Material and Methods:** A retrospective study consisting of 157 patients diagnosed for Hodgkin's disease between 1972 - 1985 and who received radiation therapy (RT) as primary treatment at Radiumhemmet, Karolinska Hospital. The general population formed the control group. The individual dose plans were reconstructed based on the individual treatment data and simulator films. Individual complication data and individual reconstructed dose volume histograms of the heart were analyzed with the use of the relative seriality model describing NTCP. The method of maximum likelihood was used to fit the individual observed complication data. The method was also analyzed grouping the material according to dose volume constraints. The method of chi-square was used for the fit.

**Results:** Of the 157 patients, 13 (8.3 %) died due to Ischemic heart disease. The Standardized Mortality Ratio (SMR) was 5.0 (95 % CI, 2.7 to 8.6).

Analysis of dose volume histograms showed an increasing risk with increasing dose to a larger volume fraction. The relative seriality model could not unambiguously model the individual observed clinical complication data. The group analysis was successful and resulted in the dose response parameters:  $D_{50} = 71$  Gy,  $\gamma = 0.96$  and  $s = 1.0$ .

**Conclusions:** A significantly increased risk of dying in Ischemic heart disease death following radiation therapy for Hodgkin's disease was found. The risk was found to increase with higher dose and larger volume fraction irradiated. No threshold effect of the dose was observed in the material. The heart was found to be less sensitive during irradiation for Hodgkin's disease compared to Breast cancer. This may be due to specific sensitive structures in the heart (e.g. left arterial descending coronary artery). Modeling of the individual clinical data proved to be hard, instead the model could describe the group data.