184 Late Rectal Toxicity: Dose-Volume Effects of Conformal Radiotherapy for Prostate Cancer

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Purpose/Objective: To identify dosimetric, anatomic, and clinical factors that correlate with late rectal complications after three-dimensional conformal radiotherapy (3D-CRT) for prostate cancer.

Materials/Methods: We retrospectively analyzed the dose volume histograms (DVH) and clinical records of 163 stage T1b-T3c prostate cancer patients who received definitive 3D-CRT without hormone therapy between 1992-1999. The patients were initially treated to 46 Gy using a conventional 4-field technique. A 6-field 3D-CRT approach was then used to boost the total isocenter dose to 74-78 Gy at 2 Gy per fraction using 18 MV photons. All late rectal complications were scored using modified RTOG and LENT criteria. Median follow-up was 62 (24-102) months. The DVHs generated from the pretreatment planning scan were analyzed to provide specific information on several dosimetric and anatomic variables. For the calculation of the DVH, the entire rectal volume was outlined.

The 6-year toxicity rate was assessed using Kaplan-Meier analysis and log-rank tests. A univariate proportional hazard regression model was used to test the correlation between Grade 2 or higher toxicity and dosimetric, anatomic, and clinical factors. For those variables found to be significant, classification and regression tree (CART) analysis was used to identify cut-points that best discriminated those patients at high risk of late toxicity. Using a multivariate proportional hazard regression model, various clinical factors were added one at a time to each dosimetric variable to determine whether the hazard would be altered by the presence of the clinical factor.

Results: The median time to developing Grade 2 or higher complications was 12 (6-72 months). The 6-year rates of Grade 2 and 3 complications were 21% and 6%, respectively. There were no Grade 4 complications.

Univariate regression analysis showed that several dosimetric variables were highly significant with respect to developing Grade 2 or higher complications. The risk of rectal toxicity increased exponentially as a function of these dosimetric variables rather than linearly. These variables included maximum dose to CTV, maximum dose to rectum, and maximum dose to rectum as a percent of the prescribed dose ($p<0.003$ for all comparisons). The percent volume of rectum irradiated to 60 Gy, 70 Gy, 75.6 Gy, and 78 Gy was found to be highly significant ($p<0.0001$ for all comparisons). The absolute volume of rectum irradiated to the higher doses of 75.6 Gy and 78 Gy was also associated with late complications ($p=0.0016$ and 0.0021, respectively). Variables that were not significant were volume of CTV, volume of rectum, and maximum dose to CTV as a percent of the prescribed dose.

For the dose-volume variables, CART analysis identified the optimal cut-points that best differentiated patients at high risk of late toxicity from those at low risk. The cut-points for the percent volume of rectum irradiated to 60 Gy, 70 Gy, 75.6 Gy, and 78 Gy were 40.6%, 26.2%, 15.8%, and 5.1%, respectively. The cut-points for the absolute volumes of rectum irradiated to 75.6 Gy and 78 Gy were 3.8 cc and 1.4 cc, respectively. The Kaplan-Meier 6-year rate of rectal complications was 54% for patients who had greater than 26.2% of rectum irradiated to 70 Gy versus 13% for those who had 26.2% or less irradiated to 70 Gy ($p<0.0001$).

Of the clinical variables tested using univariate analysis, only hemorrhoids was found to increase the risk of Grade 2 or higher toxicity ($p=0.003$). Clinical variables that were not significant were diabetes, diverticulitis, inflammatory bowel disease, and abdominal surgery. In multivariate analysis each of the clinical variables was added one at a time to the dosimetric variables. Again, only the addition of hemorrhoids was found to significantly increase the risk of late toxicity ($p<0.05$ for all comparisons).

Conclusions: DVH analyses clearly indicate a volume effect on the risk of developing late rectal complications. Therefore, dose escalation may be safely achieved by adherence to DVH constraints during treatment planning.

185 Sucralfate Versus Mesalazine Versus Hydrocortisone in the Prevention of Acute Proctitis During Conformal Radiotherapy for Prostate Carcinoma: A Randomized Study

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Purpose/Objective: To assess whether the topical use of steroids or 5-ASA is superior to topical sucralfate in preventing acute rectal toxicity during 3D conformal radiotherapy (3DCRT) to 76 Gy.

Materials/Methods: Patients undergoing 3DCRT for prostate carcinoma at our Institution were planned to be randomized to sucralfate 3 g in 15 ml suspension enema (Antepsin™, arm 1), mesalazine 4 g gel enema (Enterasyn™, arm 2) or hydrocortisone 100 mg foam enema (Colifoam™, arm 3).

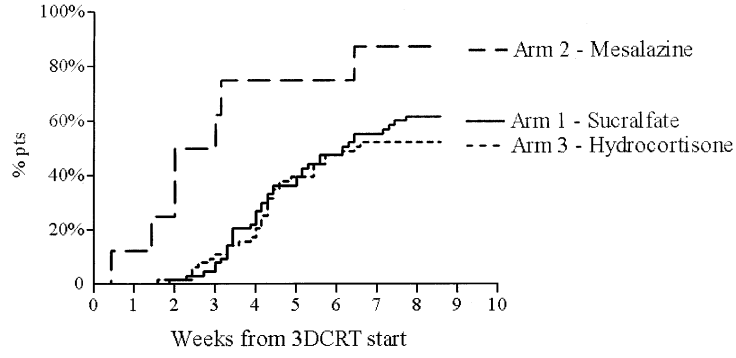
Topical treatment had to be performed once a day, starting on day 1 of 3DCRT. Patients were seen weekly during treatment and acute rectal toxicity was scored according to RTOG criteria. Time to occurrence of grade 2-3 acute rectal toxicity was taken as endpoint. For the lack of financial support, blinding was possible only to treating physician. Sucralfate was chosen in the control arm because it had not shown any benefit over placebo in a previous double-blind randomized study (O'Brien et al, R&O 45: 117, 1997). This trial was designed to detect a 20% decrease of grade 2-3 rectal toxicity (60% to 40%) with a 5% significance level, and a power of 90%. Informed consent was obtained. Analysis is based on intention-to-treat basis.

Results: The trial was open in August 1999 and after the first 24 patients had been treated, arm 2 was discontinued because of 8 patients receiving mesalazine, 7 actually developed acute rectal toxicity (5 patients grade 3 and 2 patients grade 2).

Until May 2001, 134 consecutive patients were randomly assigned to sucralfate (63 pts), mesalazine (8 pts) or hydrocortisone (63 pts). Compliance was generally good with only 7 and 6 patients of arm 1 and 3, respectively, discontinuing the assigned treatment. The cumulative incidence of acute rectal toxicity at the end of 3DCRT by arm is 61.9 ± 6.1, 87.5 ± 11.7, 52.4 ± 6.2, for arms 1, 2 and 3, respectively (figure). The difference between the mesalazine group and the sucralfate group is highly

significant (HR: 2.5; 95% CI: 1.1÷5.7, p=0.03). At both univariate and multivariate analysis taking into account several patients and treatment covariates (including rectal DVHs), the difference between hydrocortisone and sucralfate is not significant (HR=0.7; 95% CI: 0.5÷1.2, p=0.2).

Conclusions: Topical mesalazine is contraindicated during RT. Hydrocortisone enema is not superior to sucralfate in preventing acute rectal toxicity.



Cumulative incidende of Grade 2-3 acute proctitis by treatment arm

186 Predictors of Late Femoral Head Toxicity After High-Dose 3D-Conformal Radiotherapy and Intensity Modulated Radiotherapy

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Purpose/Objective: To report the incidence and identify risk factors for late femoral head toxicity and need for hip replacements (HR) among patients with clinically localized prostate cancer treated with 3-D conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT).

Materials/Methods: Between 1988 and 2001, 1684 patients were treated with conformal radiotherapy for clinical stage T1-T3 prostate cancer. Between 1988 and 1996, 912 patients were treated with a standard 6-field conformal beam arrangement. The median age in these patients was 69 years (range: 69-86 years) while the median dose was 75.6 Gy (range: 64.8-81 Gy). Beginning in 1996, IMRT was introduced, and an additional 772 patients were treated with this approach. The median dose in these patients was 81 Gy (range: 81-86.4 Gy). As part of treatment planning constraints, the femoral head dose did not exceed 68 Gy for any dose level among 3D-CRT or IMRT treated patients. The overall median follow-up to date is 65 months. The median follow-up times in 3D-CRT and IMRT groups are 35 and 96 months, respectively. All patients underwent a bone scan prior to therapy for baseline evaluation. For this analysis, all bone scan reports were retrospectively reviewed to identify the presence of abnormalities or increased uptake in the femoral head region (FHR) consistent with degenerative joint disease. A Cox regression analysis was performed to identify risk factors predicting HR in this group.

Results: Eighteen (1%) required HR after 3D-CRT. The 5-year actuarial likelihood of requiring a HR was 1%. The median time for HR after radiotherapy was 20 months (range: 3-53 months). The median age in this cohort who required HR was 71.5 years (range: 52-79 years). The dose prescription breakdown in these 18 patients was as follows: 5.5%-<70.2 Gy; 16.7%-70.2 Gy; 27.8%-75.6 Gy; 50%-81 Gy. Evidence of degenerative disease in the FHR noted on the baseline bone scans was a strong predictor of femoral head toxicity after treatment. Among 72 patients with uptake on bone scan noted in the FHR (positive bone scan), 8 (11%) required a HR compared to 10 of 1612 (0.6%) who did not have demonstrable abnormality on bone scan (p<0.001). The 5-year likelihoods of HR in positive and negative bone scan patients were 13% and 1%, respectively (p<0.001). Among patients treated with 3D-CRT, 11 of 912 (1.2%) required HR compared to 7 of 772 (0.9%) patients treated with IMRT (p=0.56). A Cox regression analysis demonstrated that a positive bone scan was the only significant predictor for HR (p<0.0001) and conferred a 15-fold increased risk for this toxicity compared to patients with negative scans.

Conclusions: The incidence of HR after high dose 3D-CRT/IMRT is low. Patients with pre-existing degenerative joint disease have a significantly higher risk of needing a HR. Although the follow up remains short, IMRT was not associated with a significantly lower risk of femoral head toxicity compared to 3D-CRT.

187 Correlation Between Radiation Dose to the Proximal Penis and the Development of Brachytherapy-Induced Erectile Dysfunction

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Purpose/Objective: Recent studies have implicated the proximal penis as a potential site-specific structure for radiation-related erectile dysfunction (ED). In this study, we evaluated whether radiation doses to the bulb of the penis and/or the proximal corporeal bodies were predictive for the development of brachytherapy-induced ED by means of a validated patient-administered questionnaire.

Materials/Methods: 30 patients who underwent permanent prostate brachytherapy and developed brachytherapy-induced ED were paired with 30 similar men who maintained potency after implantation. None of the 60 patients received supplemental external beam radiation therapy either prior to or after implantation. Potency was assessed by patient self-administration of the specific erectile questions of the International Index of Erectile Function (IIEF). The questionnaire consisted of 5 questions with