

43.6 Gy. The estimated TD<sub>50</sub> & γ<sub>50</sub> for RT Only group were 64.2 Gy & 1.58 when all the patients were included and those for subset of patients without post-RT COM were 67 Gy & 1.65. Those for Chemo+RT group were 59.7 Gy & 1.47 when all patients included and those for subset of patients without post-RT COM were 59.9 Gy & 2.02.

**Conclusions:** Post RT COM is statistically significant for incidence of SNHL. The decrease in TD<sub>5</sub> and TD<sub>10</sub> for post-RT SNHL in the dataset that included patients with post-RT COM suggest that occurrence of post-RT COM may decrease the dose for onset of post-RT SNHL. The analysis suggest that subset of patients with post-RT COM may be a high risk group for post-RT SNHL.

#### PO-0903

##### Prediction of radiation-induced toxicity in prostate cancer patients: biomarker models for nocturia and hematuria

S. De Langhe<sup>1</sup>, G. De Meerleer<sup>2</sup>, K. De Ruyck<sup>1</sup>, P. Ost<sup>2</sup>, V. Fonteyne<sup>2</sup>, W. De Neve<sup>2</sup>, H. Thierens<sup>1</sup>

<sup>1</sup>Ghent University, Department of Basic Medical Sciences, Ghent, Belgium

<sup>2</sup>Ghent University Hospital, Department of Radiation Oncology, Ghent, Belgium

**Purpose/Objective:** As most patients survive early-stage prostate cancer after treatment, quality of life outcome has emerged as an important factor to consider in treatment decisions. Radiation-induced genitourinary (GU) symptoms may impair patients' quality of life and still occur with a 5-year actuarial risk of 20%. Moreover, the incidence does not seem to plateau and may be expected many years after treatment. Therefore, the purpose of this study was to construct multi-component models for the prediction of late GU sequelae in prostate cancer patients.

**Materials and Methods:** Data were available for 265 prostate cancer patients treated with primary or post-operative intensity-modulated radiation therapy. The median follow-up was 4 years (0.5-13 years). Toxicity was scored using an in-house developed toxicity scale. For model building, clinical data (age, smoking, diabetes, hypertension, pre-treatment symptoms, transurethral resection of the prostate (TUR)), treatment data (lymph node dissection, androgen deprivation, radical prostatectomy), dosimetric parameters (doses delivered to the clinical target volume (CTV) and the bladder (B)) and 343 genetic polymorphisms were considered. Selection of parameters for the predicting model was achieved by lasso logistic regression followed by classic logistic regression for unbiased estimation of the coefficients. Missing data were handled by a stochastic expectation-maximisation (EM) algorithm. Performance of the model was expressed as the area under the curve (AUC) of the receiver operating characteristic (ROC) curve and as the false-negative rate (FNR) and false-positive rate (FPR) in the optimal point on the ROC curve.

**Results:** In our series, grade ≥ 2 nocturia and hematuria are the most prevalent GU symptoms and encompass more than 50% of the grade ≥ 2 symptoms presented. Late nocturia occurred in 29 of the 265 patients (11%). The final prediction model has an AUC of 0.81 and contains the minimal CTV dose, the CTV volume, the volume of the bladder receiving at least 65 Gy, the presence of acute grade 2 nocturia symptoms and polymorphisms rs1799983 (NOS3), rs104585 (CASP8), rs4808611 (NR2F6) and rs6163 (CYP17A1). The FNR and FPR are, respectively, 17% and 27%. A total of 14% of the patients (n=36) developed late radiation-induced hematuria. The prediction model for late hematuria has an AUC of 0.79 and consists of seven parameters: the volume of the bladder receiving at least 75 Gy, age at last follow-up visit, prior TUR and rs3931914 (HMGRC), rs2293054 (NOS1), rs708598 (PTGER2) and rs845552 (EGFR). The FNR and FPR are 28% and 29%, respectively.

**Conclusions:** Combining clinical, treatment, dosimetric and genetic factors has the potential to improve the prediction of late urinary toxicity. External validation of the prediction models is necessary before implementing these models in the clinic.

#### PO-0904

##### Genetic variants in apoptosis-related genes and radiation-induced late toxicity in prostate cancer patients

T. Langsenlehner<sup>1</sup>, E.M. Thurner<sup>1</sup>, W. Renner<sup>2</sup>, K.S. Kapp<sup>3</sup>, U. Langsenlehner<sup>4</sup>

<sup>1</sup>Medical University of Graz, Department of Radiation Oncology, Graz, Austria

<sup>2</sup>Medical University of Graz, Clinical Institute of Medical and Chemical Laboratory Diagnostics, Graz, Austria

<sup>3</sup>Medical University of Graz, Department of Therapeutic Radiology and Oncology, Graz, Austria

<sup>4</sup>Medical University of Graz, GKK Outpatient Department, Graz, Austria

**Purpose/Objective:** Fas ligand (FASL, also known as APO-1L, CD95LG, CD178, TNFSF6) triggers the apoptotic cell-death by cross-linking with its receptor FAS (TNFSF6, CD95/APO-1), and after irradiation, expression of FAS and FASL is increased and has been associated with radiation-induced delayed cell death. In the present prospective study, we analyzed the role of common polymorphisms in the genes for FAS and FASL for the development of late toxicity after radiotherapy for prostate cancer.

**Materials and Methods:** The association of FAS (-1377G>A, rs2234767 and -670A>G, rs1800682) and FASL (-844C>T, rs763110) gene polymorphisms with high-grade late rectal and/or urinary toxicity (defined as late toxicity EORTC/RTOG grade≥2) was analyzed using 607 prostate cancer patients treated with radiotherapy in curative intent. The selected polymorphisms were determined by 5'-nuclease (TaqMan) assays.

**Results:** After a median follow-up time of 81 months, high-grade late rectal and/or urinary toxicity was observed in 175 patients (29.7%). In Kaplan-Meier analysis, the -844C>T polymorphism was significantly associated with high-grade late toxicity (p=0.007). In univariate Cox proportional hazard analysis, carriers of the -844C>T polymorphism were at decreased risk of high-grade late toxicity (HR=0.686, 95%CI 0.541 - 0.87; p=0.002). In multivariate Cox regression analysis including clinical and dosimetric parameters as potential confounders, the -844C>T polymorphism in the FASL gene remained a predictive factor (HR=0.642, 95%CI 0.459 - 0.896; p=0.009). For the remaining analyzed polymorphisms no significant associations were found.

**Conclusions:** We conclude that the FASL -844C>T polymorphism may be protective against the development of high-grade late toxicity after radiotherapy for prostate cancer.

#### PO-0905

##### A predictive model for acute oral mucositis in head and neck cancer patients after primary RT, chemo- or bioradiation

H.P. Bijl<sup>1</sup>, R.J.H.M. Steenbakkers<sup>1</sup>, R. Visser<sup>1</sup>, A. Gawryszuk<sup>1</sup>, K. Wopken<sup>1</sup>, O. Chouvalova<sup>1</sup>, J.A. Langendijk<sup>1</sup>

<sup>1</sup>University Medical Center Groningen / University of Groningen, Department of Radiation Oncology, Groningen, The Netherlands

**Purpose/Objective:** Acute mucositis is a serious dose-limiting side effect during and immediately after primary RT, concurrent chemoradiation (ChemoRT) or a combination of cetuximab and accelerated RT (bioradiation or BioRT) resulting in compromised oral intake due to pain and dysphagia. The purpose of this study was to identify pre treatment variables and DVH parameters that might predict acute mucositis grade 2-4 at the end of the treatment.

**Materials and Methods:** This prospective study included 170 patients with head and neck squamous cell carcinoma (HNSSC) included in a standardized follow up program (SFP). Patients were treated with curative intent. Acute mucositis was assessed at baseline and at consecutive time points during (weekly) and after treatment. Acute mucositis was defined as grade 2-4 according the RTOG grading system. In all cases the oral cavity as well as parotid glands, submandibular glands, spinal cord and swallowing organs at risk were delineated on the planning CT scans. Dose volume histogram (DVH) parameters were collected as well as pre treatment variables. The predictive model was designed using a multiple logistic regression analysis. The primary endpoint was acute mucositis grade 2-4 assessed in the last week of the treatment.

**Results:** The predictive model consisted of the pre treatment variables: concurrent chemoradiation (coefficient=1.93) and bioradiation (coefficient=1.33). The V<sub>60</sub> (the volume of the oral cavity receiving ≤ 60 Gy) was the single statistically significant DVH parameter (coefficient=0.06) and was included in the model. The model performance was good expressed by the area under the curve (AUC = 0.83 (p=0.000)) and the Hosmer Lemeshow goodness-of-fit test (p=0.79).

**Conclusions:** The severity of acute mucositis in the last week of primary RT, ChemoRT or BioRT in head and neck cancer patients can be predicted by two pre treatment variables and one DVH parameter (V<sub>60</sub>). The use of V<sub>60</sub> can be helpful in IMRT optimization to reduce this side effect or select high-risk patients for intensified supportive care.

#### PO-0906

##### Can signs of individual radiosensitivity be seen in salivary gland scintigraphy after head and neck radiotherapy?

L. Tuomikoski<sup>1</sup>, J. Collan<sup>1</sup>, M. Kapanen<sup>1</sup>, J. Keyriläinen<sup>1</sup>, K. Saarialhti<sup>1</sup>, M. Tenhunen<sup>1</sup>

<sup>1</sup>Helsinki University Central Hospital, Department of Oncology, HUS, Finland

**Purpose/Objective:** To investigate if post-radiotherapy (RT) scintigraphy measurements of salivary glands manifest such

differences among the patients that could be explained by individual radiosensitivity.

**Materials and Methods:** The salivary gland ejection (excretion) fraction (sEF) was measured by Tc-99m pertechnetate scintigraphy for 50 patients receiving IMRT for head and neck cancer. The scintigraphy was performed before RT and repeated 6 and 12 months after RT. Only the glands with  $D_{mean}$  values between 15 Gy and 45 Gy were included and the glands which were not functioning properly prior to RT were excluded. The relative ejection fraction  $rEF(t) = sEF(t) / sEF(0)$  was first compared for both parotid glands of the same patient at the same time of measurement. Next, the rEF values at 6 and 12 months after RT were compared for the same gland. To enable the comparison of rEF values between glands receiving varying  $D_{mean}$ , the mean effect of the absorbed dose on the gland was eliminated. This was achieved by dividing the rEF value for the gland with the respective value of sigmoidal mean dose response curve for the whole group of patients ( $rEF_0 = rEF(t) * (1 + (D_{mean}/D_{50})^k)$ ). Fisher's exact test was used in the analysis with two categories defined by median  $rEF_0$ . Average errors in  $D_{mean}$  values for the glands due to patient positioning errors were corrected based on portal images.

**Results:** The values for  $rEF_0$  ranged from 0 to 2.7. A significant association between  $rEF_0$  for left and right parotid glands was found ( $\chi^2=6.0, p<0.025$ ). Some patients show systematically lower or higher  $rEF_0$  than the median for both parotid glands. This could be explained by three possible reasons, as the effect of positioning errors to  $D_{mean}$  was excluded: 1) the variations result from the measurement technique or 2) the patients react differently to the lemon juice stimulus given during the scintigraphy or 3) the post-RT sEF is affected by varying individual responses to radiation. The  $rEF_0$  values for the same gland at 6 and 12 months after RT gave a statistically significant relationship between the two variables ( $\chi^2=4.73, p<0.05$ ) (Table 1). The same patients had low or high values of  $rEF_0$  for both parotid glands at both times of measurement. As this behaviour is seen in both measurements, it can not be due to fluctuations caused by measurement technique. Also, we believe that by using relative values instead of single sEF values, we can at least partly overcome the problem of patients reacting differently to the stimulus, assuming that the factors, such as smoking, that may influence saliva production remain the same between the measurements. As a result of this indirect deduction, we conclude that the systematic variation in  $rEF_0$  reflects individual differences in radiosensitivity.

	$rEF_0(6\text{ months})$ below median	$rEF_0(6\text{ months})$ above/equal to median	Total
$rEF_0(12\text{ months})$ below median	18	10	28
$rEF_0(12\text{ months})$ above/equal to median	12	21	33
Total	30	31	61

**Conclusions:** According to our interpretation the systematic variations seen in post-RT salivary gland scintigraphy measurements can be explained by individual differences in radiosensitivity. Quantitative extraction of individual radiosensitivity requires further studies.

**PO-0907**

**Magnetic ferrofluid hyperthermia for breast cancer treatment**

I. Marinova<sup>1</sup>, V. Mateev<sup>1</sup>, A. Chakarova<sup>2</sup>

<sup>1</sup>Technical University of Sofia, Department of Electrical Apparatus, Sofia, Bulgaria

<sup>2</sup>National Hospital of Oncology, Department of Radiotherapy, Sofia, Bulgaria

**Purpose/Objective:** Ferrofluid particles being subjected to an electromagnetic field show remarkable heating effects related to losses during the magnetization process and Joule heating of the particles. The temperature enhancement which occurs in a magnetic ferrofluid system under the influence of an external high frequency magnetic field has found applications in breast tumor hyperthermia treatment therapy. The main objectives are the uniformity of the temperature distribution and the target value of temperature to be up

to 42°C in the controlled region for magnetic hyperthermia treatment. This temperature control is hard to implement because of many tissue individual variations and other therapy conditions.

**Materials and Methods:** For determination of the thermal field distribution in magnetic hyperthermia therapy, a coupled electromagnetic - thermal - fluid dynamics field computational model is developed. The electromagnetic field distribution inside the conductive tissue region depends on the time varying magnetic flux density. The heat sources are defined by the electric losses in tissue, acquired by the solution of the electromagnetic field problem. The computational model uses anatomically precise multilevel geometrical model of human breast with known electrical tissue properties, blood and liquor flow speeds in its vessels. Model contains information about real cancer structure sample acquired by surgical procedure. Cancer and normal electrical tissue properties are directly measured for this sample by precise measurement system.

**Results:** Sample under treatment is in stage T2N2M1 with maximal size of 25 mm. Sample volume is 317 mm<sup>3</sup>. Ferrofluid solution is injected at cancer sample. Ferrofluid filled volume in sample is 24 mm<sup>3</sup>. Thermal field distribution in cancer model is presented in Fig.1. Maximal temperature acquired is 42.3°C. Temperature maximum represents the position of ferrofluid volume. Results from this model are validated by infrared thermography measurements of the sample. Field values and distributions correspond well to these one acquired by the model.

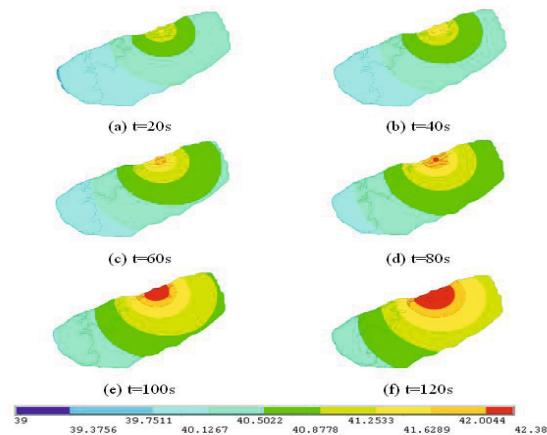


Fig.1 Thermal field distribution in tumor model for time period of 120s.

**Conclusions:** The coupled electromagnetic-fluid dynamics-thermal field computational modeling is capable to predict the magnetic ferrofluid hyperthermia thermal effects on live tissue. The developed model can be used for therapy planning and also design and optimization of interaction between electromagnetic devices and biological structures.

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**PO-0908**

**Identification of a single nucleotide polymorphism associated with sexual dysfunction in prostate cancer patients**

J.H. Oh<sup>1</sup>, R. Stoyanova<sup>2</sup>, J.O. Deasy<sup>1</sup>, Z. Saleh<sup>1</sup>, M.K. Buyyounouski<sup>3</sup>, R.A. Price<sup>3</sup>, J.J. Hu<sup>4</sup>, A. Pollack<sup>2</sup>

<sup>1</sup>Memorial Sloan-Kettering Cancer Center, Medical Physics, New York, USA

<sup>2</sup>University of Miami, Department of Radiation Oncology, Miami, USA

<sup>3</sup>Fox Chase Cancer Center, Department of Radiation Oncology, Philadelphia, USA

<sup>4</sup>University of Miami, Department of Epidemiology and Public Health, Miami, USA

**Purpose/Objective:** To study whether genetic single nucleotide polymorphisms (SNPs) are predictive of erectile dysfunction (ED) in prostate cancer patients treated with radiotherapy, we investigated the relationship between genotypes in SNP data and Expanded Prostate Cancer Index Composite (EPIC) scores.

**Materials and Methods:** In our previous study, we examined SNPs obtained for 124 prostate cancer patients who received radiotherapy (RT) and, after identifying a statistically-managable number of SNPs using a novel system biology approach, we identified a single SNP (rs2032809) that was statistically associated with post-RT adverse