Radiotoxicity in prostate cancer: The first radiogenomic Spanish GWAS

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Introduction. Despite improvements in radiotherapy techniques, a substantial percentage of prostate cancer patients treated with external beam radiotherapy still suffer from clinically relevant radio-induced toxicity. Variability in radiotherapy response is mainly due to dosimetric factors, additional treatments and patient characteristics. However, nowadays there is increasing evidence supporting the heritability of this phenotype. Most studies attempting to unravel the genetic background of radio-induced toxicity, following a candidate gene approach, have been unable to replicate previous findings.

Objective. We aimed to identify new loci associated with the development of radio-induced toxicity through a genome-wide association approach. Methods Samples were obtained from 735 unselected Galician (NW Spain) prostate cancer patients treated at the Radiation Oncology Department of the Clinical University Hospital of Santiago de Compostela from 2006 to 2011 (RADIOGEN study). Morbidity was prospectively documented using the Common Terminology Criteria for Adverse Events v3.0. Standardised total average toxicity (STAT) score was derived to assess acute and late overall toxicity. Univariate analyses were performed by linear regression by comparison of allele frequencies, and covariates, with overall acute or late STAT scores. Multivariate analyses of overall acute and late toxicity included those covariates with univariate p-values lower than 0.05. Multivariate linear regression residuals were calculated for each patient to quantify the non-accounted toxicity by the available covariates.

Results. Nineteen covariates were included into the multivariate model for acute toxicity, while the late toxicity model was defined by three covariates, being the most significant the previous report of acute toxicity. After quality data assessment 552,597 markers were evaluated. From these, seven and eighteen loci showed p-values lower than 0.05 for the development of acute and late radio-induced toxicity, respectively.

Conclusions. We have identified new genetic loci associated with overall radiotherapy toxicity by using a genome wide association design. These results must be replicated in an independent cohort to be validated.

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Recap: Outcomes in patients with intermediate risk prostate cancer

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Objectives. The aim of this study is to assess the biochemical non-evidence of disease survival (bNEDs), disease free survival (DFS), and overall survival (OS) rates, as well as, to identify some of prognostic factors associated with this outcomes in intermediate risk prostate cancer patients in the context of a multi-institutional Spanish database (RECAP).

Materials/methods. Patient selection was according NCCN criteria and all of patients were treated with external beam radiotherapy. Related variables included age, PSA, Gleason score, cT stage, number of positive cores, Androgen Deprivation Therapy (ADT) and external radiation dose.

Results. A total of 1878 patients were included. Median age was 71 years (range: 47–86). Mean initial PSA was 10.24 ng/ml (range 6–20 ng/ml). Clinical stage T1 and T2 was 35% and 65%, respectively. 25% had Gleason score 6 and 75% Gleason score 7. Median radiation dose to prostate was 74 Gy (range: 66–76 Gy) and 76% of patients received ADT. With a median follow-up of 61 months, the 5-year and 10-year bNEDs was 92% and 78% respectively, 96 and 89% DFS and 98% and 95% for OS. There were not grade 3 GI or GU acute and late toxicity. Multivariate analysis to determine independent prognostic factors for biochemical control will be presented after the last follow-up.
Conclusions. This is a large multi-institutional retrospective Spanish data base (RECAP) study of intermediate risk prostate cancer patients treated with external beam radiation therapy. Outcomes (biochemical control and survival) are high, with a low incidence of acute and late toxicity.

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Reduced toxicity in intraprostatic fiducial-guided IMRT for localized prostate cancer

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Background. IMRT allows higher doses being delivered to the prostate gland sparing organs at risk and as a result, it is increasingly used to treat localized prostate cancer (LPC). There is, however, concern about increased risks of late toxicity.

Purpose. To report acute and late gastrointestinal (GI) and genitourinary (GU) toxicity after 79.6 Gy delivered with IMRT in LPC, and to evaluate predictors of treatment-related toxicity.

Methods and materials. Consecutive 671 patients with LPC cT1-3 stages were treated with dose-escalation radiotherapy from 1999 to 2011. Inclusion criteria included: no previous pelvic radiotherapy, radiation dose > 72 Gy and minimum follow-up > 12 months. 437 patients were treated with three-dimensional conformal radiotherapy (3DCRT) and 234 with IMRT/IGRT using intra-prostate gold fiducial markers. Median dose was 78.6 Gy and 76.9 Gy, respectively. Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events 4.0. Analyses were carried out using SPSS 17.0.

Results. Median follow-up for the entire cohort was 58 months (range, 12–170 months). Compared to 3DCRT, overall toxicity was lower in the IMRT group. Grade 2 or higher complications were very low: 4.8% acute GI, 14.5% acute GU, 3% late GI and 3% late GU. Late rectal bleeding in the 3DCRT and IMRT was 7.1% and 2.6%, respectively (p = 0.015). Multivariate analysis showed that intraprostatic fiducial-guided IMRT (odds ratio = 0.628, p = 0.018) and presence of rectal symptoms during RT (odds ratio = 2.314, p = 0.000) correlated with GI late toxicity.

Conclusions. High-dose IMRT with intraprostatic fiducial markers has a significantly lower rate of GI and GU complications compared to 3DCRT. The presence of acute rectal toxicity can predict a higher risk of late GI toxicity.

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Relation dose volume histograms and quality of life in prostate cancer

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Purpose. Few studies have evaluated the relation between dose–volume histograms (DVH) and toxicity in prostate cancer and even fewer studies have studied the association between DVH and health-related quality of life (HRQL). The aim of this study was to assess the correlation between DVH in organs at risk (OAR) outcomes as measured with specific HRQL questionnaire Methodology. Between January 2003 and November 2005 a total of 190 patients with clinically localized prostate cancer were recruited in Catalan Institute of Oncology to participate in a multicentric study of HRQL following radical prostatectomy, external beam radiotherapy and prostate brachytherapy treatment for clinically localized prostate cancer. Inclusion criteria were stages T1 or T2 and low risk prostate cancer. HRQL was evaluated by two generic questionnaire (SF-36, FACT-G) and several specific questionnaire (FACT-P, EPIC, IPSS and IEEF). DVH for OARs (penile bulb, rectum and bladder) were created for 119 of the 190 patients to assess the correlation between DVH and HRQL using Functional Data Analysis.

Results. The distribution dose–volume (DDV) in the rectum was higher in patients with faecal blood and loose stools compared to patients without such toxicity when the DDV was between 0–40 Gy and 20–70 Gy respectively. At all points on the bladder DDV curve, the DDV was higher in patients with urinary incontinence than in patients without toxicity. We found no relation between the presence of Urinary obstructive side effects and the DDV. Although many patients had Sexual function impairment, we found no association between this side effect and penile bulb DDV.

Conclusion. The results of his study suggest that the entire range of the dose volume curve must be considered to assess correlation between the histogram and quality of life, because correlations could appear only in a limited part of the DVH. Functional Data Analysis was a valuable tool to properly analyze the DVH data. These results could help radiation-oncologists to select the best treatment from among the various treatment strategies in order to achieve the best quality of life outcomes.

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