Scientific Symposium (Mon, 21 Sep, 16:15−18:15)
GENEPI: genetic prediction of radiation damage − where do we stand?

60 INVITED

GENEPI-ENTB 2: an infrastructure for the individualisation of radiotherapy

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GENEPI-ENTB (Genetic Pathways for the Prediction of the effects of irradiation) – the European Normal and Tumour tissue Bank and database was initiated in 2003 by ESTRO (European Society for Therapeutic Radiology and Oncology) as a pan-European bio bank and database to facilitate research in the response to radiation, more particularly in the genetic determinants of the variation in individual radiation sensitivity. The capacity of the bio bank is still expected to be double before the end of the current FP6 project (Grant agreement FI6R 036437), supported by EURATOM.
Patient, tumour and treatment related data are entered in a central database linked to the distributed tissue banks where DNA containing material of these patients, collected before the start of treatment, is stored. Outcome is prospectively and actuarially assessed and for a subset of patients the treatment plan information is accessible in the central database. Radiotherapy related side effects are carefully documented for a minimum period of five years. The focus is on the main tumour sites: breast, lung, prostate, head and neck and rectum. Tissues and data on patients showing extreme reactions to radiotherapy are stored in a separate database (so called 'overreactors').
At this moment the prospect of reaching the goals set out in the GENEPI-ENTB 2 project is excellent. There are 35 users of the new database, which is operational since 04–2008. The database shows significant improvements in clinical data input and user-friendliness in comparison with GENEPI-1. Data on 6905 radiotherapy patients have been collected; more than 11.000 tissues have been obtained. Thanks to the anticipated bulk import (by the centres Maastricht, Dresden, Aarhus, Royal Marsden and Christie Hospital) an additional input of 7720 data is foreseen in the near future. Ten overreactors (from Canada and EU countries) have been identified and stored in a separate database.
The GENEPI Consortium and its partners hope that GENEPI-ENTB 2 will be able to make a substantial contribution to research leading to the identification of high-risk patients. This would allow clinicians to tailor the dose to the individual radiosensitivity of each patient and improve the cost-effectiveness of high-tech radiotherapy aimed at avoiding complications.

61 INVITED

Low dose cell responses – predictors of normal tissue damage after radiotherapy?

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Although recent advances in radiation delivery have significantly reduced the risk and severity of skin fibrosis, ~5−10% of patients receiving radiotherapy still suffer from normal tissue damage which seriously affects quality of life. Attempts to link normal tissue responses in patients and various phenol-typical cell and molecular responses to high (greater than 2.0 Gy) *in vitro* doses have generally been unsuccessful. Potentially, the high doses used previously could be masking a low dose effect. Furthermore, the pattern of gene expression induced by low dose radiation is very different from that seen at high doses.
The aim of the GENEPI-lowRT project is to explore links between the development of severe, normal tissue complications following radiotherapy with various pheno-typical responses and genetic pathways induced at low radiation doses. The project comprises 7 European clinical and basic science laboratories who are addressing whether changes in genetic and functional responses induced at low doses in either fibroblasts or T-cells derived from breast cancer patients correlate with the severity of patients' normal tissue responses.
Linking the GENEPI database (www.genepi-estro.org) with the levels of genetic changes induced at low dose provides an ideal opportunity to address whether genetic differences between individuals are associated with the development of severe, normal tissue complications. The possibility of tailoring dose prescription to the individual radiosensitivity of each patient could indeed be a quantum step forward in decreasing adverse effects of radiation. Progress on the project which is ongoing, will be presented.
The knowledge obtained from this combination of approaches will help assess if low dose effects can be used to quantify non-cancer health risks and identify potential genetic components of occupational, environmental and medical exposure to radiation. Additionally knowledge of individual genetic predisposition to late effects of ionizing radiation contributes to evaluation of health risk of low dose radiation.
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Genetic markers of normal tissue effects after radiotherapy

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The ultimate goal of curative radiotherapy is to inactivate all tumor cells without severely damaging the surrounding normal tissue so as to provide a high quality of life for the patient. However, for many tumors, the applicable dose and therefore the chance of cure is limited by the risk of side effects. Therefore, there is a great need to establish methods that can be used to predict the individual risk of normal tissue effects after radiotherapy.
It was shown by us that the kinetics of late effects are best described by an annual probability, p_a, to develop this side effect. This value might vary between 1 and 15% per year. The variation was considered mainly to result from differences in the individual radiosensitivity. The individual radiosensitivity was found to be best determined by scoring the number of chromosomal deletions in lymphocytes irradiated in vitro with 6 Gy. Study with monozygotic twins revealed that this sensitivity is mostly determined by genetic factors.
For breast cancer patients this parameter was found to show a broad variation with a CV of about 15%. When this distribution was used to classify patients into three groups (resistant, normal or sensitive), there was a clear increase in the annual risk of fibrosis with increasing sensitivity. A similar association was seen, when individual sensitivity was associated with the risk of acute effects.
In a recent study risk of acute or late effects were associated with single nucleotide polymorphisms (SNPs) present in genes that relevant for the induction (GSTP1, SOD2) or repair (ATM, TGFβ1, XPD, XRCC1) of DNA damage induced by ionising irradiation. It was found that the risk of fibrosis was higher in patients being polymorphic in *TGFβ1* (position −509) or *XRCC1* (codon 399), when compared to patients with wild type genotype, whereas for *ATM* (codon 1853) and *GSTP1* (codon 105) the non-polymorphic genotyp was associated with a higher risk of fibrosis. Although these associations were only of borderline significance ($p = 0.06$−0.26), a statistically significant increase in risk of fibrosis with increasing numbers of risk alleles was found, when combinations of these four polymorphisms were analyzed ($p = 0.003$). However, none of the six polymorphisms, were found to have a clear effect on the individual radiosensitivity as assessed via chromosomal damage ($p = 0.3$−0.7). A similar observation was made for the risk of acute effects, where SNPs in TGFβ1 and XPD were associated with a higher risk. These data indicate that a combination of specific polymorphisms, which do not have a clear effect on individual radiosensitivity, can be used to predict the risk of late or acute affects after breast conserving radiotherapy.

63 INVITED

Gene level and epigenetic predictors

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During the last decade, a number of studies have supported the hypothesis that there is an important genetic component to the observed interpatient variability in normal tissue toxicity after radiotherapy. Genetic markers with sufficient predictive power to be used at an individual level have not been identified yet. Although it is still an open question whether such markers can be identified, some progress has been made recently, particularly, for predicting late toxicity. Some of the more promising predictive assays are based on lymphocytes or fibroblasts. Commonly following in vitro irradiation, gene expression profiles are measured or functional assays are recorded and used to identify individuals with low or high risk of normal tissue toxicity. Although the technical set-up for these assays makes it unlikely that they will enter any routine clinical settings, they have allowed the identification of genes that are involved in the development of radiation induced morbidity. These genes, or the pathways in which they are functioning, could be relevant targets for intervention