## *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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**62** INVITED

**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

and might also lead to the identification of candidate genes for single nucleotide polymorphism (SNP) association studies. So far, most of the SNP association studies reported have been limited by the inclusion of a small number of investigated genes and low numbers of patients with different kinds of normal tissue toxicity. Future genetic association studies will be equally impeded by the difficulties in identifying relevant candidate genes, characterising well-defined clinical and biological phenotypes, and handling of the many confounding factors. International collaborations to assemble appropriate cohorts and technological developments (like the ESTRO GENEPI project) will hopefully lead to the identification of potential markers and assays, and validation of genetic markers through the use of candidate gene approaches and whole genome association studies.

## *Scientific Symposium* (Mon, 21 Sep, 16:15−18:15)
## After cancer therapy, prevention and promotion

**64** INVITED

**Optimal approaches to post treatment recovery: multidisciplinary team working**

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Most survivors of adult cancers will not experience serious long term effects of cancer treatment but even with the best modern surgery, radiotherapy, hormone and biological treatments, it is not possible to cure cancer without the risk of damage to normal tissues.
In the UK alone it is estimated that there are currently 500,000 people experiencing a long term effect with an adverse effect on health and well being.
Some problems start during treatment and resolve within a few weeks or months, others begin during treatment and persist, still others may not appear until months or years later. This long time frame offers challenges to characterizing populations with particular needs, describing and populating care pathways and developing the teams with the competency to respond to different levels of need. There are challenges in supporting and educating primary care, both to detect and manage new chronic survivorship conditions and to recognize the increased incidence and severity of common chronic conditions (e.g. cardiovascular disease, diabetes and osteoporosis). Establishing and testing specialist multidisciplinary services for those with the most severe complex multi organ effects is particularly difficult in the current financial climate. Testing through the UK NCRI consequences of cancer treatment workstream has suggested some early learning.

**65** INVITED

**Exercise for disease prevention and health promotion in cancer survivors**

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**Background:** The transition from primary cancer treatment to survivorship can be a challenging one marked by chronic and late effects such as functional limitations, fatigue, psychosocial distress, poor quality of life (QoL), weight gain, disease recurrence, and increased risk of other chronic diseases. These challenges have generated interest in behavioral strategies that might improve QoL, reduce the risk of disease recurrence, and extend survival in cancer survivors. One lifestyle factor that has received significant research attention is exercise or physical activity (PA). The purpose of this presentation is to provide an overview of research examining the effects of PA on supportive care and disease endpoints in cancer survivors that have completed primary treatments.
**Materials and Methods:** An overview of the literature of previous exercise intervention trials and observational studies conducted during the survivorship phase.
**Results:** Several recent meta-analysis have summarized the research on PA and supportive care endpoints in cancer survivors. These systematic reviews have reported favorable effects of PA interventions on physical fitness, quality of life, fatigue, and psychosocial outcomes. Interestingly, these reviews have observed that the effects of PA interventions on supportive care endpoints may be larger during the survivorship phase compared with the adjuvant treatment phase. This finding is important given that 50% of cancer survivors indicate that they would prefer to start a PA program after they have completed their primary treatments. Most studies to date have focused on breast cancer survivors, however, several recent observational studies using cross-sectional designs have reported positive associations between PA and QoL in understudied cancer survivor groups such as multiple myeloma, brain, ovarian, endometrial, bladder, colorectal, lung, and non-Hodgkin lymphoma but few randomized trials have been conducted in these groups. Within the last five years, researchers have begun to examine the association between postdiagnosis PA and disease endpoints in cancer survivors. Several recent large epidemiologic studies have shown that higher levels of PA are associated with a lower risk of disease recurrence, cancer-specific mortality, and longer survival in breast and colon cancer survivors. Nevertheless, all of the studies to date are based on observational data.
**Conclusions:** Overall, research indicates that PA interventions are safe and feasible for several cancer survivor groups and result in favorable improvements in physical fitness, QoL, fatigue, and psychosocial outcomes. More recently, prospective observational studies have provided evidence for an association between PA and disease endpoints but the causal role of PA on disease outcomes has not been established. In Canada and Australia, we have launched the Colon Health and Life-Long Exercise Change (CHALLENGE) trial, which is a multinational, multicenter randomized controlled trial designed to determine the effects of a 3 year structured PA intervention on disease-free survival in stage II and III colon cancer survivors who have completed adjuvant therapy within the previous 2−6 months. If this research confirms that PA improves disease-free survival in colon cancer survivors, there will be a strong case for implementing PA programs in the cancer setting to improve both QoL and disease outcomes.

**66** INVITED

**Assessment of young adult survivors needs: building an evidence-based late effects service**

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There is now strong evidence from late mortality and morbidity studies to support the establishment of late effects services for childhood, adolescent and young adult cancer survivors. The requirements of the service are more difficult to determine. Cancer survivor's needs change over time. This is influenced by at least two factors. Firstly cancer determined factors like the patients age at diagnosis, the treatment received, the interval from end of treatment, and the natural history of late sequelae. Secondly the age of the survivor at follow-up, whether still a child, adolescence or adult and their expectations.
The aim of a late effects service is to enable the survivor to reach their maximum potential in all aspects of a multidimensional quality of life. To enable this to occur, input is important from multidisciplinary teams, survivors, their families and the community. From a medical perspective the aims of follow-up are to detect late effects early and treat as necessary. To educate survivors regarding self management to help decrease the effects of treatment. The degree of input from health care professionals varies enormously from minimal follow-up to hospital based multispecialist clinics depending on the risk and type of late sequelae. The provision of care needs to be flexible and individualised for each survivor.
Assessment of needs must involve survivors. Reports from focus group work with survivors have all highlighted the need for comprehensible information regarding late effects of treatment from knowledgeable health care professionals with good communication skills. They often state that they wish to be in control of their follow-up care but are aware that their involvement with professionals will vary. They want the ability to make contact with a key worker in the late effects service as required and for many it is important to move on in their lives and leave their medical history behind.
The evidence for the need of a late effects service is present but to date there are no studies on the cost benefits of such a service. More research is needed to assess different models of care and to determine the effects of new treatments.

**67** INVITED

**Managing late effects following haematological malignancy and BMT**

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**Background:** More than 40,000 haematopoietic stem cell transplants (HSCTs) are performed worldwide each year and with improvement in technology and care more patients now survive. However there are late complications that can cause substantial morbidity. Furthermore HSCT poses significant challenges to the surviving patient's longer-term adjustment due to the frequent, ongoing presence of treatment late effects and vulnerabilities. Late effects include chronic Graft versus Host Disease (cGvHD), immune deficiency, lung, liver, cardiac, endocrine, dental and ocular effects, sexual dysfunction, osteoporosis, hypercholesteraemia, secondary malignancies and late graft failure. Functionally, patients experience significant fatigue and weakness and consequent difficulties with resuming work, family and leisure activities. Psychologically, recovering from the