Several challenges need to be addressed before a gene expression profile can be approved as a predictive biomarker by regulatory bodies like the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). In an ongoing trial, EORTC-1219 (ClinicalTrials.gov ID: NCT01880359), a 15-gene hypoxia profile (1,2) is being tested prospectively. One of the primary aims of the study is to provide data for regulatory approval of the gene profile as an accompanying biomarker for the use of the hypoxia modifier Nimorazole. The development and ongoing validation of this 15-gene profile will be used as a general example of the challenges for implementing gene expression profiles in PRO. Different strategies for identification of relevant gene expression profiles will be discussed together with the challenges of validating the predictive value of a gene expression profile. The requirements for a quick and robust test for the gene expression profile working on simple routine FFPE (formalin-fixed, paraffin-embedded) sections will also be discussed. Finally, some of the regulatory and patent issues related to gene expression profiles will be commented upon.


SP-0580
GWAS, SNPs and normal tissue toxicity for personalised radiation oncology
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A key challenge in radiotherapy is to maximise radiation doses to cancer while minimising damage to surrounding healthy tissues. As toxicity in a minority of patients limits the doses that can be safely given to the majority, there is interest in developing a test to measure an individual's radiosensitivity before treatment and predict their likelihood of developing toxicity. A biomarker that predicts a cancer patient's risk of toxicity could be used to personalise dose prescriptions or to offer alternative treatments. Many approaches have been studied to measure radiosensitivity. The development of omics technologies underpinned genome wide association studies (GWAS) attempting to identify genetic variants reported as single nucleotide polymorphisms (SNPs). The advantages of the approach include: a genetic test will be easier to implement clinically than a functional assay; a genetic test will not suffer from the poor reproducibility associated with some radiosensitivity testing methods; and SNPs are the most common type of genetic variation and so easiest to identify. Omics technologies offer promise, but to have an impact on radiotherapy practice research must identify biomarkers that replicate across cohorts. Robust replication needs big data, which is only possible with large collaborative efforts. The need for big data was addressed by establishing an international Radiogenomics Consortium. Achievements of the consortium include: pooling cohorts to increase statistical power and identify definitively whether individual SNPs are associated with risk of toxicity; producing guidelines to improve the reporting of radiogenomics studies; identifying approaches for analysing data from heterogeneous cohorts involving different toxicity reporting scales and treatment regimens; and establishing studies collecting standardised data to improve our ability to detect more SNPs. Work over the past three years showed it is possible to pool heterogeneous cohorts and has identified several SNPs associated with risk of toxicity. Large collaborative projects in the cancer predisposition field involving analysis of ~100,000 participants shows that sufficient SNPs can be identified to generate a polygenic risk profile for clinical implementation. For example, men in the top 1% of the distribution of a 74-SNP polygenic risk score have a 4.7 fold increased risk of developing prostate cancer. Key challenges for the radiation oncology field are to collect data to enable the cancers to identify enough SNPs to generate a polygenic risk profile and to increase understanding of the need for endpoint dependent versus independent profiles.

SP-0581
Integrative data analysis for PRO
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Personalized Radiation Oncology (PRO) integrating omics technology is a rapidly developing concept that will have an enormous impact on oncologic treatments and specifically radiation therapy in the near future. Tumor behaviour and outcomes related to oncologic treatments are related to several factors of which connections are nowadays poorly known. Different branches of medicine have developed their own lines of research which are sometimes difficult to be interpreted, difficult to be integrative with classical clinical factors and for these reasons difficult to be transformed into clinical practice. In clinical prediction and decision making process, results provided by omics are rarely used, whereas clinicians usually use clinical and imaging data for understanding tumor behaviour, predicting patients' outcomes and for choosing the most suitable treatment. The clinical decision is usually based on general guidelines which extrapolate information from randomized clinical trial. Moreover independent factors derived from several RCT are used by the Radiation Oncologist to make his prevision on tumor behaviour and consequently to choose the "right treatment" for a specific patient. Randomized clinical trials enclose patients with characteristics chosen beforehand and usually omics informations are rarely or never included. This lead to a potential missing of several information that could refine prediction and thus promote personalized treatments and to an erroneous outcome prediction that can lead to an inappropriate treatment decision for a specific patient. Integrative data analysis has the potential to correlate data of different origins (genetic, radiology, clinic…) with patient's outcomes and to create a consistent dataset useful to obtain a trustful analysis for the Decision Support System. The DSS can easily be applied in clinical practice helping the Radiation Oncologist to utilize several information that otherwise would be excluded in the process of decision making. The possibility to predict the outcome for a certain patient in combination with a specific treatment with more accuracy, will lead to better identification of risk groups and thus better treatment decisions in individual patients, but it will also stimulate research focused on specific risk groups which try to find new treatment options or other combinations of treatment options for these subgroups. These treatments will be more personalized, which will not only save patients from unnecessary toxicity and inconvenience, but will also facilitate the choice of the most appropriate treatment. The resulting predictive models, based on patient features, enable a more patient specific selection from the treatment options menu and a possibility to share decisions with patients based on an objective evaluation of risks and benefits. Finally, considering the important role that predictive models could play in the clinical practice, clinicians must be aware of the limits of these prediction models. They need to be internally validated taking into account the quality of the collected data. An external validation of models is also essential to support general applicability of the prediction model. Therefore structural collaboration between different groups is crucial to generate enough anonymized large databases from patients included or not in clinical trials.

OC-0582
Gene signatures predict loco-regional control after postoperative radiochemotherapy in HNSCC
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