is organised at national level, in close collaboration between ASN and radiotherapy professionals, leading to the publication of newsletters about the safety of patients.
Taking into account one of the main findings of the international conference on Modern Radiotherapy, organised in 2009, by ASN, in Versailles (France), the European Commission decided to strengthen the European Basic Safety Standard introducing new requirements related to events reporting and risk analysis, and to launch the ACCIRAD project led by the Greater Poland Cancer Centre (GPCC, Poland)[1], following the goal to issue an European guidance on these topics in 2013. A general questionnaire sent to member states in 2012 showed that more than half EU countries have already implemented in their legal system a requirement for risk analysis in radiotherapy, and classification, recording and reporting of adverse events and near misses. However, despite 15 years passed since 1997, in many EU countries the requirement for a legal framework regarding risk analysis and event's classification, recording and reporting systems was not addressed and the practical implementation of the systems was still incomplete.A 2nd questionnaire, still being analysed, should allow to identify pertinent risk analysis methodologies used by radiotherapy centres and also good practices for event's classification. On this basis, recommendations will be prepared by the ACCIRAD consortium to be included in the European guidance. The first results of these on going works will be presented at the Geneva ESTRO conference in April 2013.

## SYMPOSIUM: ADVANCED METHODS FOR TOXICITY PREDICTIVE MODELS

**SP-0396**
**Machine learning approaches to modelling dose-volume effects.**
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Characterising the dose-volume response of normal tissue structures is an important part of optimising radiotherapy treatment planning. However, understanding how the dose-distribution to a structure is related to outcome is confounded by co-morbidities and combinations of treatments as well as incomplete and inconsistent data. One approach to this challenge is Machine Learning. Machine learning describes models which learn from examples of a specific data type without *a priori* information about the relationship between the data.
When both input variables and the corresponding outcome data are available, this known as supervised learning. Once the relationship has been inferred it is possible to make prediction for previously unseen cases.
The published literature on the use of machine learning approaches to model dose-volume effects utilise different algorithms. Two commonly used supervised learning approaches are Artificial Neural Networks and Support Vector Machines.
Artificial Neural Networks (ANN) are a (simplified) mathematical analogy of learning in the brain. An ANN is trained by presenting example datasets to the network. Input variables are propagated through a network of interconnected nodes and compared to the known outcome. The weights of the connections between the nodes are altered iteratively so that the outcome is predicted correctly from the input data.
Support vector machines (SVM) are used for dichotomised outcomes e.g. toxicity/no toxicity. Separation between the two possible classes is achieved by translating the input variables in to a high-dimensional feature space where a boundary is derived to maximise the separation between the classes.
An important consideration when developing a machine learning-based model is how to represent the input data. This issue is not unique to machine learning and is also relevant to conventional statistical approaches. When trying to predict radiation-induced toxicity the dose distribution to relevant structures need to be included. Generally this is achieved by using summary measures such maximum dose and mean dose to the structure. The dose-volume histogram can be reduced to a summary measure such as Equivalent Uniform Dose (EUD). Often sequential variables describing the volume of the structure receiving a specified dose eg V5, V10, V15 etc are included.
A more detailed approach is to include a spatial description of the dose. These dosimetric features will be combined with clinical information and information regarding other therapies such as chemotherapy.
A successful model will be able to make predictions for previously unseen data. Cross validation, where models are built on subsets of available data and tested and validated on independent samples, can ensure the ability of a model to generalise. The effect of each variable on the ability of a model to make accurate predictions can be assessed with methods such as "leave one out" which as suggested repeats the process without a variable and assess the effect.
This presentation will provide an overview of published literature on the modelling of dose-volume effects using machine learning. A worked example of both ANN and SVM approaches to predict acute toxicity following head and neck radiotherapy will be used to demonstrate methodology. The results will also be compared to a conventional multivariable analysis.
Relatively little has been published on the use of machine learning approaches to the modelling of dose-volume effects. However, they provide a complementary alternative to conventional statistical techniques. Consequently there is potential to further our understanding of the relationship between the dose distribution to a normal structure and corresponding radiation-induced toxicity.

**SP-0397**
**Including clinical (and genetic) covariates in NTCP models**
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It is well known that the risk of radio-induced toxicity increases when higher doses and larger volumes are involved in the irradiation and, in the last years, some consistent results have been published on the possible estimation of normal tissue complication probability (NTCP) for a number of organs-at-risk. The widespread method used for such calculations is based on a sigmoid dose-response curve coupled to reduction of the whole dose-volume histogram into one parameter (such as the equivalent uniform dose).
NTCP models with their prediction based only on dosimetric variables can be used in treatment planning and can act as a baseline reference.
On the other hand, it is becoming clearer that radiation-related side effects are also correlated to a number of patient-related factors. With the advent of newer radiotherapy technologies, which allow steep gradients and minimization of doses to normal tissues, there is an increased interest in understanding clinical/genetic risk factors that might enhance patient radio-sensitivity and to develop NTCP models which might include these variables in order to achieve better normal tissue complication predictions.
Some recently published studies have shown that current NTCP models can be improved by incorporating clinical risk factors into model formulation. Overview of published results will be presented.
A further important step is the inclusion of molecular/genetic predictors into NTCP models. This issue is still at a very primitive stage and should be elucidated because, given the same set of clinical/dosimetric factors, patient-to patient variability in normal tissue response to radiation has been widely recognized in clinical practice, suggesting that this phenomenon might be, at least in part, genetically driven.
In this presentation data on molecular/genetic markers influencing radio-induced toxicity are presented, together with the first findings supporting the hypothesis that a genetically determined dose–response relationship is possible and could be used to predict the probability of side effects associated with radiotherapy and serve as a rational basis for individualized radiation dose prescriptions.
The future lies in these multi-factorial prediction models: a great effort has to be done to collect reliable detailed prospective data for the development of NTCP models with the inclusion of predisposing clinical/geneticfeatures for normal tissues involved in radiotherapy.

**SP-0398**
**An image-based approach to investigate sensitive tissues related to trismus following head and neck radiotherapy**
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Trismus, which results in difficulty, restriction or pain when opening the mouth (CTCAE), is a common complication in head and neck cancer patients following radiotherapy and leads to degradation in quality of life. There are few studies that have addressed radiation induced trismus. However, the main cause remains poorly understood. Studies have attributed trismus to the irradiation of a range of organs at risk (OAR) such as the mastication muscles, the temporomandibular joint (TMJ), and pterygoid plate among others.