

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/genetic features 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.

Current normal tissue complication probability (NTCP) models rely heavily on dosimetric parameters that are derived from dose-volume histograms (DVHs) which lack the spatial information. These parameters assume a homogenous response to radiation and tend to ignore any inter or intra-organ variation in radiosensitivity. To address these issues in our analysis, we developed an image-based approach which utilizes the full 3D dose distribution and does not assume any prior knowledge of the OARs. Using image registration, we deformed CT scans, anatomic structures, and 3D dose distributions from a patient cohort onto the same frame of reference "standard patient". Voxel-based correlations between dose and the complication endpoint (trismus) were computed over the entire voxel space to construct a 3D correlation map.

We applied this methodology to a cohort of 110 oropharyngeal cancer (OPC) patients treated with IMRT and Chemotherapy at MSKCC between 2004 and 2009. The results showed a good agreement between the image-based approach and the standard NTCP models. Both approaches showed a statistically significant correlation between the dose to mastication muscles and trismus. Furthermore, the voxel-wise 3D correlation map provided additional information and revealed regions of high correlation outside the mastication muscle region which might suggest the involvement of other organs or tissues at risk. However, the clinical implication of these new findings needs further investigation in an independent data set and might be related to beam arrangement and configuration.

In addition, we also developed a new metric to estimate the geometric uncertainty of the underlying deformable registration which we denote as distance discordance (DD). More technical details and a few examples will be presented to illustrate the concept of DD and its impact on the uncertainty of dose mapping. In summary, this study demonstrates the validity of this approach and emphasizes the need to consider the full 3D dose distribution in conjunction with DVH analysis.

SYMPOSIUM: FLATTENING FILTER FREE LINACS

SP-0399

FFF and new dosimetric challenges

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Many new treatment units are already on the market that operate without a flattening filter (FF) or can be operated in a dedicated clinical flattening filter free (FFF) mode, i.e. Tomotherapy, Cyberknife, Varian's True-Beam or ELEKTA's Agility linacs, respectively. The commonly accepted dosimetric benefits of FFF high energy photon beams, which range from increased dose rate and dose per pulse, to favorable output ratio in-air variation with field size, reduced energy variation across the beam, reduced leakage and out-of-field dose, respectively, imply new dosimetric challenges. These are related to beam quality specification, beam calibration, small field dosimetry, acceptance testing/commissioning, regular quality assurance procedures, and finally treatment plan verification. As far as the acquisition of basic relative beam parameters is concerned, the commissioning of a FFF treatment delivery unit is not very different from a standard linac. However, the increased dose rate and the high dose per pulse needs to be considered, since some point detectors show a pronounced dose rate dependency (e.g. diamond detector, liquid filled ionization chamber), possible saturation or reduced collection efficiency.

The forward peaked dose distribution of FFF beams is fundamentally different and makes standard parameters as used for quality control of linacs, e.g. homogeneity, field flatness and beam penumbra, not always viable. Recently suggestions have been made to overcome this issue in clinical dosimetry.

Small field dosimetry is of special importance since all relevant clinical applications of FFF beams are closely related to high precision radiotherapy techniques, i.e. stereotactic RT or IMRT, where small fields/segments build the basis for treatment delivery.

Today's challenge of small beam dosimetry and its link to absorbed dose determination in reference geometry is enhanced by unflattened beams and dedicated high precision radiotherapy delivery units that do not allow to setup the reference conditions, as defined by the IAEA TRS 398 or AAPM TG 51 codes of practice. Incorrectly measured beam output in small beams can result in systematic uncertainties when implementing basic beam data in treatment planning systems (TPS), misleading results in acceptance testing/ commissioning of a TPS, and finally erroneous patient treatments leading to radiation incidents or accidents. Therefore correction factors for a variety of commercially

available small ion chambers and other radiation detectors are currently being investigated in order to extend their use towards small beam dosimetry in FFF photon beams.

The accuracy of dose calculation in TPS represents another dosimetric aspect. Several studies demonstrated that inverse planning tools for IMRT are able to handle unflattened beams and that the dose calculation accuracy of commercial TPS is not impaired when removing the FF.

SP-0400

Flattening Filter Free beams: treatment planning

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The advent of the Flattening Filter Free beams (FFF) available on common linacs, is facing the community to the ability of treatment planning system to accurately model such beams, and with the understanding of which are the best sites and treatments which could take advantages from using FFF beams. An overview of the published data on dose calculation algorithms accuracy for FFF fields is given.

The characteristics of the FFF beams are here analyzed to evaluate the clinical sites where such beams could take advantage. The main characteristics relate to the out-of-field dose (peripheral dose) that could lower the organs at risk dose; to the high dose rate, allowing shorter treatment time for stereotactical treatments; to the profile shape that could be better suitable for small targets or simultaneous integrated boost treatments.

A review of published planning studies presents plan comparisons in different sites. Prostate, lung, brain, head and neck plans were evaluated for IMRT treatment with different beams (6 and 18 MV, flattened and unflattened). Also whole breast plans (with different techniques from tangents to IMRT) and esophageal treatment (conformal, IMRT, VMAT) were analysed by different groups. Results of such studies presenting rather large volumes showed no significant difference in plan quality between standard flattened and FFF beams. A substantial reduction of MUs and consequently of radiation outside the target was evidenced for most of sites, although the opposite could be found for very large (or very elongated) targets, where the lower off-axis dose would play an unbeneficial role.

The lower radiation dose outside the target was also studied on anthropomorphic phantom to simulate pediatric IMRT treatments with FFF beams in the intracranial regions. The measured dose reduction in the periphery (from thyroid to ovaries and testes) was lower of 23 to 70% relative to the standard flattened beams.

Particular attention is paid to stereotactical treatments, where the high dose rate is the clear and natural benefit in treating with FFF beams. Studied sites were early stage lung treatments, liver metastases and pelvic/abdominal metastases.

Examples of lung and brain stereotactical comparisons with and without flattening filter are given.

Conclusions: there are benefits in using FFF beams for some treatment site and lesion sizes. The primary benefit is, for high dose per fraction treatments, the high dose rate that reduces the beam-on time. Other proven benefits are the lower out-of-field and peripheral dose, that decrease the critical structures dose and the risk of secondary cancer induction.

SP-0401

Radiobiology implications of Flattening Filter Free treatments

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Flattening filter free (FFF) options are now commercially available and treatments utilising the higher dose-rates obtained are being introduced into clinical use. Removal of the flattening filter results in an increase, by a factor of 2-6 times, in the instantaneous dose-rate of the x-ray pulse compared to the standard flattened beams. The increased dose per pulse, result in an equivalent increase in the average dose-rate and a potentially similar reduction in overall treatment time. The potential radiobiological factors that result from changing the instantaneous dose-rate include potential changes to sub-lethal damage repair mechanisms, potential synergistic effects and the potential radiobiological effects resulting from changes to the overall treatment time. A number of *in-vitro* studies have been undertaken using x-ray beams from linear accelerators designed specifically to study the implications of changes in dose-rate of the treatment beams resulting from treating with flattening filter free beams. These studies have used a variety of experimental methodologies to achieve the required instantaneous dose-rates and differing ways to ensure dose uniformity over the *in-vitro* flask. These differences in the experimental methodologies have not led to