pneumonitis. Patients with minimum grade 2 were considered as RP.

Results: Composite perfusion changes were associated with dose. Statistically significant dose-dependent reduction in regional perfusion was observed at 3, 6 and 12 months FU. Comparison of dose-response curves based on their slopes showed a dose-dependent reduction in perfusion at all time intervals (R2=0.8-0.9) except 1 month (R2=0.4). Relative perfusion loss per dose bin was 4% at 1 month, 14% at 3 months, 13% at 6 months and 21% at 12 months FU (Figure 1).

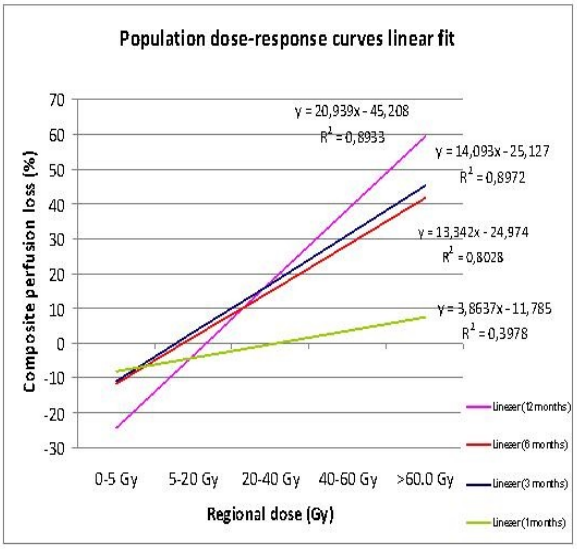

Figure 1. Dose-response curves linear fit for composite perfusion changes 1, 3, 6 and 12 months after radiotherapy

The dose-response relations varied between patients with or without RP. In patients who developed RP, perfusion reduction was larger in 20-40 Gy dose bin at 3 months FU (p=0.04), and in >60 Gy dose bin at 6 months (p=0.03), compared to those without the complication. Low dose regions, on the contrary, revealed larger perfusion increase at 12 months FU in the patients with RP (p=0.002).

Conclusion: Progressive dose dependent perfusion loss was seen on SPECT up to 12 months following IMRT. Patients with radiation pneumonitis demonstrate a larger perfusion loss in the high dose regions, as well as relatively larger perfusion increase in regions receiving low dose, possibly due to function being shunted to these areas.

OC-0382

A novel concept to tumour targeting: inverse dose-painting or targeting the "Low uptake drug volume"

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Purpose or Objective: There are several potentially radioresistant targets for dose escalation in dose-painting apporoach. Among them tumor hypoxia is a very attractive target. However, 2-3 times higher radiation dose is required to overcome hypoxia-mediated radioresistance in tumors, which is clinically difficult to achieve due to normal tissues constraints. Therefore, we propose a novel treatment approach to combine 1) targeting hypoxic tumor cells with a hypoxia-activated prodrug (HAP) TH302 and 2) at the same time use inverse radiation dose-painting strategy to boost tumor subvolumes with no/low drug uptake. We tested this approach in a rat rhabdomyosarcoma model using 18F-HX4 hypoxia tracer, which is a surrogate of TH302 accumulation in a tumor.

Material and Methods: A clinical PET/CT scanner was used to evaluate 18F-HX4 uptake 3 hrs post injection. Low or high drug uptake volume (LDUV or HDUV) was defined as 40% of the GTV with the highest or the lowest 18F-HX4 uptake, i.e. TH302 accumulation. Within 24 hrs after PET/CT animals (n=9) received either a single dose radiotherapy (RT) uniformly or a dose-painted non-uniform irradiation with 50% higher dose to LDUV or to HDUV. Mean dose in uniform RT was 18.5 Gy similarly to the mean dose in DUV. Mean dose to the GTV in the non-uniform RT scenario was 14.9 Gy. Treatment plans were created using Eclipse treatment planning system. Animals were irradiated on a TrueBeam High Definition 120 Leaf MLC linac. Tumor response was quantified as time required to reach 3-times starting tumor volume (TGTV3).

Results: Non-uniform RT with radiation boost to tumor subvolumes with low TH302 uptake (LDUV) was much more effective than the same dose escalation to subvolumes with high drug uptake (Fig. 1). Noteworthy, dose escalation to LDUV was as effective as uniform RT with 3.6 Gy higher mean dose to GTV.

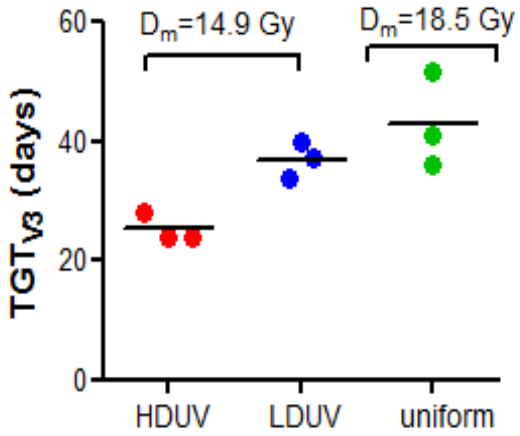

Fig. 1.Time to reach 3-times starting tumor volume (TGTV3) after uniform RT or non-uniform RT with dose escalation to tumor volume with high drug uptake (HDUV) or low drug uptake (LDUV). Mean dose (Dm) to GTV is indicated.

Conclusion: The results of this pilot study support targeted dose escalation in non-hypoxic tumor subvolumes with no/low accumulation of hypoxia-activated prodrugs, which requires further confirmation. This strategy appears to be as effective as a uniform dose escalation of the entire GTV but with greater capacity to spare normal tissues. It is expected that this approach of inverse dose-painting can be combined with other imageable cytotoxic drugs, which warrants further investigations.

Teaching Lecture: How to bring QUANTEC into the 21st century?

SP-0383

How to bring QUANTEC into the 21st century?

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The implicit concept behind the title of this lecture concerns the role of “quantitative” data-driven approaches in assessing dose-volume effects in normal tissues in the era of “high-tech” radiotherapy and integration of “omics”. The continuously growing literature regarding dose-volume relationships indirectly reflects the need of improving and refining our knowledge in this field [1]. This seems to be particularly urgent in a number of clinically relevant situations such as, for instance, heart, bowel and bladder. However, the impact of the above mentioned elements (“high-tech & “omics”) on the research issues of this field is increasingly relevant and claims for the development of new research lines and methods that will shortly be overviewed in the lecture.

The occurrence of radiation-induced toxicity is a very complex process that is always modulated by the individual [2]; if two patients receive the "same dose distribution" they will likely have different reactions and possibly one will experience toxicity while the other not. The availability of individual information potentially characterizing the patient response, including the "omics" information, is highly valuable, especially in the "high-tech" era of image-guided/adaptive IMRT in which organs are more efficiently spared: the better sparing reduces the incidence and severity of toxicities and, at the same time, enhances the impact of individual sensitivity factors. This point reinforces the need to create large data bases including individually assessed clinical, biological and genetic information, in addition to the individual dose distribution. As a consequence, the approach of quantitatively modelling dose-volume relationships is increasingly becoming "phenomenological" [3]: robust methods for (dosimetric and non-dosimetric) variable selection able to condense the information in "reliable", friendly to use, predictive models is a major field of research: the adaptation of statistical methods for data-mining and to avoid over-fitting is a pivotal point of the story.

Although the potentials of large data bases and of data sharing platforms on toxicity modelling are clear [4], we should not forget that the creation of large data-bases is not the "aim" but is a (powerful) "tool". The outcome of the process in terms of robustness and reliability of the models will not only depend on the "numbers" (a highly important component) but also (and maybe more importantly) on the "quality" of data. Differently from the "easy" score of the success of a therapy (survival, tumour control), toxicity is a much more complex issue that deserves specific attention and the careful collection of patient-reported and/or physician-reported information, often for years. Well assessed prospective observational studies focused on specific toxicities seem to be the best choice; secondary analyses of high-quality data coming from controlled trials are also very important although they may be limited in some cases by too homogenous protocols restricting the spread of the delivered dose distributions.

At the end of the circle, the external validation of integrated dose-volume models is clearly a crucial component of the next year's research [3]: testing the generalizability of dose-volume models will be a major end-points. In addition, robust results from phenomenological models are expected to feed up mechanistic approaches in a sort of mutual synergy that can further corroborate our knowledge: these two components (mechanistic and phenomenological) will likely cooperate much more in the next future. Relevant developments are expected to impact the quantitative modelling of normal tissue effects also from the side of the dosimetry data. The robust, organ-planning-DVH approach to quantitatively describe the relationship between dose/volume and toxicities should be overcome/refined in many relevant situations by directly looking to the 3D dose distribution, integrating the spatial information lost when using "classical" surrogates like DVH/EUD. Relevant examples are: the direct measurement of dose-map dissimilarities between patients [5], the quantification of local (and organ) effects by imaging biomarkers [6], the interplay between the dose received by different organs, the impact of anatomy changes during therapy and their incorporation into normal tissue predictive models.

Quantitative modelling of normal tissue effects is lively present in current century and seems to have a brilliant future in contributing to rapidly improve the way we treat our patients with the promise to continuously reduce toxicity.

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2-Bentzen SM. Nature Rev Cancer. 2006;6:702-713
3-van der Schaaf A et al. Int J Radiat Oncol Biol Phys 2015;91:468-471
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Teaching Lecture: Shared decision making

SP-0384
Shared decision making
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Drawing on experience as a practicing GP with a special interest in communication skills and shared decision making, the work of The Health Foundation funded MAGIC (Making Good decisions in Collaboration) programme and most recently on a collaboration with a Danish Oncology Hospital, Dr Dave Tomson will explore recent developments in Shared Decision Making (SDM). Using experience and expertise from the delegates we will

a) check out attitudes and beliefs about the need and rationale for putting SDM centre stage in patient interactions,
b) look at a useful model of SDM both for personal clinical practice and for teaching other clinicians,
c) explore some of the key skills needed and the key challenges in doing better SDM with a particular focus on oncology – the constant changing nature of the evidence base, individualised care in a guideline driven world, dealing with personal bias, unwarranted versus warranted variation in practice, the tyranny of time.
d) share some ideas about possible solutions to these challenges and think about some of the steps needed to both develop personal practice and implement programmes of development within departments and across hospital systems

Teaching Lecture: The study of therapy resistance in genetically engineered mouse models for BRCA1-mutated breast cancer

SP-0385
The study of therapy resistance in genetically engineered mouse models for BRCA1-mutated breast cancer
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Although various effective anti-cancer treatments have become available over the last decades, therapy resistance remains the major cause of death of cancer patients. Striking examples are patients with tumors that are defective in DNA repair by homologous recombination (HR). Despite initial responses to cancer therapy, resistance of primary or disseminated tumors eventually emerges, which minimizes therapeutic options and greatly reduces survival. The molecular mechanisms underlying this therapy escape are often poorly understood.

A clinically relevant mechanism for the defect in HR is a lack of function of BRCA1. This defect impairs error-free repair of DNA double-strand breaks (DSB) – a feature that can be exploited by the treatment with DSB-inducing agents. Using the *K14cre,Brca1F/F,p53F/F* (KB1P) genetically engineered mouse model for BRCA1-mutated breast cancer, we have shown the success of this strategy. Tumors are highly sensitive to DNA cross-linking agents, or to the inhibition of topoisomerase I/II and poly (ADP-ribose) polymerase (PARP) (reviewed by Rottenberg & Borst, 2012). Despite this sensitivity, tumors are not eradicated and eventually drug-refractory tumors emerge. In several of the resistant tumors we found that the HR defect can be partially rescued by down-regulation or knock-out of additional repair factors, such as 53BP1 (Jaspers *et al.* 2013) or REV7 (Xu *et al.* 2015).

Based on these observations we set out to investigate whether this type of HR restoration can also explain radiotherapy resistance. For this purpose, we treated mice carrying KB1P tumors with high-precision radiotherapy. We