The aim of radiotherapy is to eradicate cancer, while at the same time minimizing the side effects. Although important improvements in imaging and radiotherapy techniques have enabled better target definitions and radiotherapy delivery, normal tissues are always exposed to radiation to some degree. Side effects thus still occur, but their variable degree, even when corrected for dosimetric characteristics, suggests that common genetic variants may play a role. However, similar to other human traits, radiosensitivity is considered to be a complex polygenic phenotype determined by the interaction of multiple loci.

Identifying these genetic markers will further enable precision radiotherapy in which the optimal treatment plan will take into account the genetic pre-disposition to toxicity (and of the tumour). It should not be assumed that all of the phenotypic variation is due to germ line genetic variation, but that that epigenetic changes (inherited and acquired) could also be important, including variants in mitochondrial DNA.

In response to the lack of success of candidate gene SNP studies in small studies, the focus of radiogenomics has shifted towards GWAS and big data research within international networks (1). At the same time, effort was made to establish standardized methods for reporting on radiogenomics (2). In recent years, remarkable progress has been made in the field of radiogenomics, of which some examples are cited.

Single nucleotide polymorphism genotypes were determined in female breast cancer patients from the RAPPER study, showing that patients with a high polygenic predisposition to breast cancer do not have an increased risk of radiotherapy toxicity, but that individual variants may increase risk (3). Identifying SNPs in oxidative stress-related genes associated with risk of late toxicities in breast cancer patients receiving radiation therapy, a variant allele in the base excision repair gene XRCC1 was found that could be used in combination with additional variants to predict late toxicities (4). A GWAS study in 1742 prostate cancer patients treated with external beam radiotherapy identified the TAN1C locus (that has a role in regenerating damaged muscle) to be of significant importance in the development of late radiation-induced damage (5). It is expected that these and other improvements in genotyping together with better phenotyping of patients will be incorporated in treatment planning, decision support systems and drug development to increase the therapeutic ratio of radiotherapy.

Keywords: radiogenomics, side effects

Acknowledgement: This project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no 601826 (REQUIRE).

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References:

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Combinaison of an anti HPV-E7 vaccine to radiotherapy: preclinical data in a head and neck model.


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of HPV-associated head and neck squamous cell carcinoma (HNSSC). The efficacy of the irradiation and vaccine association was tested using a model of HNSSC obtained by grafting TC-1/luciferase cells at a submucosal site of the inner lip of immunocompetent mice. Irradiation and the STXB-E7 vaccine acted synergistically with both single and fractionated irradiation schemes, resulting in complete tumor clearance in the majority of the treated mice. A dose threshold of 7.5 Gy was required to elicit the dramatic antitumor response. The combined treatment induced high levels of tumor-infiltrating, antigen-specific CD8(+) T cells, which were required to trigger the antitumor activity. Treatment with STXB-E7 and irradiation induced CD8(+) T-cell memory, which was sufficient to exert complete antitumor responses in both local recurrences and distant metastases. We also report for the first time that a combination therapy based on local irradiation and vaccination induces an increased pericyte coverage (as shown by cSMA and NG2 staining) and ICAM-1 expression on vessels. This was associated with enhanced intratumoral vascular permeability that correlated with the antitumor response, suggesting that the combination therapy could also act through an increased accessibility for immune cells. The combination strategy proposed here offers a promising approach that could potentially be transferred into clinical trials. The implementation of selective immunomodulatory approaches during the treatment of HPV positive tumors could eventually lead to increase anti tumor efficacy with favorable tumor versus normal tissue differential effect.

Keywords: HPV, STXB-E7 vaccine, radiation, mice

References:

65 How emerging trends in basic research & technology will shape clinical research? E. Deutsch1,2,3

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Radiation therapy is an ever changing discipline and technology. It has made unprecedented improvements with the incorporation of concurrent chemotherapy regimens which translated into local control and survival gains. The improvements of beam delivery techniques have led to decreases in morbidity following treatment. We are now facing an important wave of changing concepts which profoundly impact our understanding of the basic mechanism of oncology which have had profound consequences on the perception of the biology of response to radiotherapy having both consequences for tumor and normal tissues. Interestingly these changes do not replace former concepts but rather contribute to broaden the scope of radiation biology. Direct radiation induced cell kill of tumor clonogens has now to be integrated within the concept of microenvironment. The overwhelming contribution of tumor hypoxia remains un disputed but the concept of microenvironment by itself now implies the contribution of several cellular compartments which are shown to contribute to both tumor response and the generation of normal tissue damage. These findings have paved the way for a new generation of combination of clinical trials which are now emerging. The possibility that immune modilation during the course of radiotherapy could not only have impact on local control but also on distant disease is a fascinating paradigm. Technology for treatment and imaging have in parallel considerably evolved, leading to increased precision and targeting possibilities widening the use of stereotactic radiotherapy which constitutes a major change for the management of primary and secondary tumors. Routine integration of biomarkers in our tumor rounds such as HPV status for head and neck and 1p19q for brain tumors are examples of the integration of the concept of precision medicine into radiotherapy and other examples should follow.

Functional imaging and the latest developments of image texture analysis will contribute to increase the level of precision of our treatments, define the areas at risk for relapse but these images might also contain valuable biological information. Practical examples of clinical trials using novel technologies (nanoparticles), biomarkers selection and oligometastatic disease, will be used to present the practical integration and the challenges represented by these novel concepts into the clinic.

Keywords: Oligometastasis, clinical trial, immune therapy, targeted therapies, biomarkers, functional imaging.

66 First tests to implement an in-house 3d-printed photon bolus procedure using clinical treatment planning system data. G. Dipasquale1, R. Miralbell1, P. Starkov2, O. Ratib2

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Purpose: Additive manufacturing is becoming of interest in Radiotherapy especially for bolus creation. This study aimed to develop an in-house procedure to print photon bolus created with the treatment planning system (TPS) using small sized printers, cost effective, and logistically easy to implement in RT departments.

Material/methods: A fused deposition modeling (FDM) printer with a heated bed plate (Rova3D, Ordsolutions, Ontario, Canada), was used together with Poly-Lactic-Acid (PLA) material. Using as TPS Eclipse® version 13 (Varian Medical Systems, Palo Alto, California) a plan was created on a Rando® head phantom CT scan and a “digital” bolus created in the eye region with Hounsfield Units (HU) of 140, corresponding to PLA printed density of 1.12 g/cc. This bolus was exported from Eclipse and converted in STL file. Bolus creation and printing took approximately 1 hour. To verify the form of the 3D-printed bolus, its HU, and dose distribution obtained when using it, the latter was positioned on the head phantom and a CT scan was acquired. Two plans with anterior-posterior fields and 6 MV X-ray beams were created using either the “digital” or the 3D-printed bolus and plans were compared. To measure and compare the dose distribution, skin layers of 3 mm and 5 mm thickness were created, just beneath the bolus, as well as a target simulating a tumor reaching the body surface (see figure). The analytical anisotropic algorithm was used for dose calculation with a grid size of 1 mm.

Results: The first 3D-printed bolus contained some air bubbles, and had a smaller thickness (less than 0.1 cm) but properly reproduced the form (see figure). The printed bolus presented in its solid portion a density of 140-150 HU with values as low as ~450 HU in the bubble regions and a mean ± SD value of 32 ± 154 HU. Dosimetric comparison showed good agreement on mean doses and max doses, while volumes receiving 95% of the prescribed dose differed by ~6% for all structures with 3D-printed bolus plans showing more coverage, (see table).

Conclusion: In conclusion, first dosimetric results look promising and further tests will be implemented to improve the bolus filling and the erosion of the surface, as well as to investigate the possibility to use soft PLA materials (likely more comfortable for patients). More sophisticated, realistic patient’s plans should be tested and in vivo thermo luminescence dosimetry should be used for treatment plan verification.