Radiobiology shapes the future of radiation oncology, ENLIGHT meeting 2019

At the 2019 annual meeting of the European Network for Light ion Hadron Therapy (ENLIGHT), hosted by the University of Caen (Normandy, France) and the centre for cancer treatment at Caen, Centre François Baclesse, from 1-3 July, experts from all over the world gathered to discuss the hottest topics in radiation oncology. While a significant part of the discussion focused on quality assurance issues, a hot topic of the meeting was radiobiology, including the novel FLASH technique.

A talk entitled **FLASH Effect** was presented by Dr Jean Bourhis (CHUV, Lausanne). He offered a very comprehensive review of the history of the concept that was 'almost' discovered in 1967, but rediscovered recently by Vincent Favaudon et al. (Institut Curie-Recherche, Orsay, France). The fundamental dose-rate requirements to observe a genuine FLASH effect have been soundly defined: a high dose per fraction is required (in the order of 8Gy to 10 Gy) delivered in a very short time of about 100ms to 200 ms to reach about 100 Gy/s as a dose rate. Hyper-oxygenation wipes out the effect, which does not seem to exist for tumours. The audience was reminded of the preclinical data obtained on animal models and the treatment of the first patient. Although the consistent use of FLASH is not yet defined, these data are really exciting, and FLASH will surely be part of the future of radiation oncology.

Jean Bourhis explaining the FLASH effect

Further insights into the FLASH effect were given by Kevin Prise (Queen's University Belfast), including clues regarding a relationship between oxygen depletion and FLASH effect. Prof Prise also gave a nice overview of proton FLASH, which showed that the pristine observations on lung fibrosis and dermatitis could be reproduced, but some other healthy tissue animal models did not show the FLASH effect (Zebra fish). Interestingly, proton FLASH is dramatically reducing the number of modulated genes, senescent cells or over-expression of transforming growth factor (TGF) beta compared with conventional irradiation. The anti-tumour effect does not appear to be modified.

The discussion continued with Andrea Mairani (HIT-CNAO). He showed a comprehensive analytical **dose-calculation engine** based on parallel graphics processing unit (GPU) computing with pencil-beam-splitting approach. It was developed in 2017 at HIT and CNAO. Using as input the characteristics of the treatment planning system (TPS) beam, it is able to calculate many different aspects of ion beam treatment, such as physical dose, linear energy transfer (LET), and relative biological effectiveness (RBE) using different models for all available ions at HIT (1H, 4He, 12C, 16O), multi-ions, hypoxia, etc. It is intended to reach accuracy similar to that of Monte Carlo (MC) (compared and validated against the Monte Carlo simulation package FLUKA) with clinical viable calculation times that are about 200 times shorter than those performed with FLUKA MC code. The FRoG package has been implemented in four centres currently: HIT, CNAO, the Danish Centre for Proton Therapy at Aarhus and the CYCLotron for HADron therapy centre (CYCLHAD) in Caen, France. Stewart Mein, who is doctoral fellow in the Mairani group at HIT, was one of the poster awardees for his contribution to this project.

Along the same lines, a highlight of this session was **the *NanOx model***, presented in detail for the first time by Michael Beuve (IPN Lyon). This new model of cellular radiation-dose effect, developed in Lyon by a strong collaboration between physics and biology, is a fully stochastic model based on a full description, although simplified, of the global effect of ionising radiation on living cells. Five cellular parameters are needed to model the cell response to any type of IR: nuclear size of the cells, α-ref and β-ref (photons), α-ion high LET and α-ion intermediate LET. Comparisons have been made with reference cell lines (V79, CHO-K1 and HSG), different ion beams (P, He, C, Ne and Ar) and biological effectiveness models MKM and LEM I, II, III and IV. Good agreement has been obtained with better (χ)2 scores than MKM and LEM. Clinical applications are now foreseen.

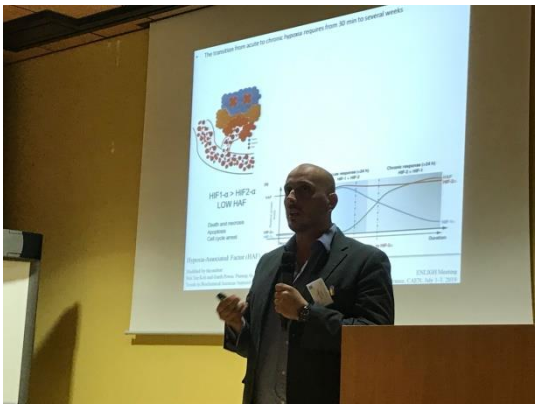
Gerd Datzmann (Munchen) presented convincing preclinical data regarding a modern adaptation of the grid concept to protons. No particles are lost, since the pristine beam is focused into microbeams of 100 µm Ø, and 6000 Gy/beam equivalent to an average of 60 Gy per fraction in a continuous volume. This beam structure spares the entrance tissues better than 10 Gy X-rays when studied in an

animal model. The technological challenges were detailed as well as a possible solution with a proton linac (ADAM design). The entrance of the use of **nanoparticles in clinical practice** was confirmed by Jacques Balosso (Grenoble and Caen), who presented the first in-human application of gadolinium-based nanoparticles for the treatment of multiple brain metastases. A phase I trial was completed in 2018 in Grenoble University Hospital. This nanoparticle treatment, named AGuiX®, is presently part of several phase II clinical trials that include randomised protocols. Proton therapy will be improved by such treatment, since despite efforts to spare tissue from damage, organs at risk that are embedded inside a tumour can only be further spared by increasing the differential effect. This is the purpose of the use of nanoparticles in radiotherapy.

Jacques Balosso, one of the local organisers, spoke on nanoparticles.

Claire Rodriguez-Lafrasse of the University of Lyon, France, gave an overview of 17 years of radiobiology research devoted to **heavy ions and radio-resistance**. These works were initiated in the framework of ETOILE, a project to promote the construction of a national cancer treatment centre at Lyon, then continued under the follow-up project France HADRON. This part of the research required irradiations in multiple centres: the Grand Accélérateur National d'Ions Lourds (GANIL, known in English as the National Large Heavy Ion Accelerator) in Caen; the German research facility GSI, and the National Institute of Radiological Sciences (NIRS) in Chiba, Japan. Results regarding extrinsic apoptosis pathways, telomerase sensitivity, specific aspects regarding cancer stem cells and more recent very exciting approaches on hypoxia and non-hypoxia differential hypoxia inducible factor (HIF) induction were presented. A convincing concept of the stealthy damage ('stealth-bomber effect') of carbon ions compared with low LET radiations was illustrated. The translational purpose of all these findings was emphasised.

Is hypoxia sensitive to particle therapy? This question was tackled by Walter Tinganelli (GSI), who showed participants a set of experimental and modelled results obtained at GSI with the TRIP98 code package and multiple ion beam treatment planning system (TRIP98-MIBO TPS). Dose adaptation to take account of hypoxia is undoubtedly efficient at killing hypoxic cells, and use of a combination of ions of different LETs is able to optimise the dose reduction in the immediate vicinity of the tumour if heavier ions, such as ^{16}O, are used for the dose boosting in the hypoxic centre of the tumour model. However, as mentioned, these mixed beams must be reproducible in each treatment session, the dose plan must be calculable and reliable information is needed regarding the site and depth of the hypoxia in tumours.



Walter Tinganelli explaining hypoxia

Paul Lesueur (CFB, Caen) has been a good strong advocate of the use of poly-adenosine diphosphate ribose polymerase (**PARP) inhibitor** as a combined treatment with radiation. As PARPs are partners in the recombination repair of complex DNA damage, use of high LET radiation would be expected to improve results. Early results are validating a strong combined effect in vitro and clinical trials are ongoing. The team is also investigating the fascinating use of PARP inhibitor to trigger so called 'synthetic lethality' in BRCA1 or BRCA2-mutated tumour cells.

Manjit Dosanjh (ENLIGHT, CERN) gave a presentation on future requirements and research direction for particle radiobiology on behalf of Working Party 6 of the European Particle Therapy Network (EPTN) on the training day. The session showed that radiobiology is not only alive but thriving.

All presentations are available at https://indico.cern.ch/event/783037/timetable/#all.detailed

The presentations were followed by a visit to the CYCLHAD facility in Caen, France.

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