IRENE VETRUGNO

Laboratory for Applied Radiobiology

Department of Radiation Oncology, Institute of Physiology
University of Zurich
Winterthurerstrasse 190, 8057 Zürich

irene.vetrugno@uzh.ch
https://www.physiol.uzh.ch/en/research/integration/grpruschy.html

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UNRAVELING A NOVEL CONCEPT OF FRACTIONATED RADIOTHERAPY FOR THE TREATMENT OF SOLID TUMORS

Intensity-modulated radiotherapy, advanced computer technology and imaging techniques achieved impressive results in therapeutic radiation oncology during the past decade. Ideally, radiotherapy treatment delivers a high dose to the tumor while sparing the surrounding healthy tissues and organs at risk from radiation damage. There is now extensive ongoing research investigating how complex mathematical models can be implemented into the clinics in order to precisely shape the radiation dose to the tumor while shielding normal tissues. Alongside, the focus of radiotherapy on inducing lethal DNA damage in cancer cells has been recently shifted on acknowledging the pivotal role of the biological effects triggered by ionizing radiation in the tumor microenvironment (TME) in co-determining radiotherapy treatment outcomes. Particularly, TME has been defined as "game changer" in radiotherapy.

In this project we investigate an innovative concept of fractionated radiation therapy called spatiotemporal fractionation. According to this approach, different dose distributions are delivered to complementary parts of the tumor in order to achieve high doses to the target while ensuring a low dose-bath in normal tissues. Spatiotemporal fractionation is based on the assumption derived by the Biologically Effective Dose (BED) model that different parts of the tumor can be treated in different fractions as long as by locally adding up the doses delivered to each fraction the prescribed BED is achieved in the tumor. Our main purpose is to achieve an end-to-end validation of this hypothesis to potentially bring forward spatiotemporal fractionation on the preclinical level. By using an image-guided high precision small animal radiotherapy platform, we will assess the projected benefit of spatiotemporal fractionation in experimental murine tumor models, while unraveling the biological role of the immune system in the antitumoral response. Furthermore, we will use a sensitive reporter system to detect changes of tumor hypoxia *in vivo* in the context of spatiotemporal fractionation schemes.

In addition to that, we will investigate the validity of another important derivation of the BED model, according to which different fractionation schemes with an equivalent BED will lead to the same clinical effect regardless of the chosen number of fractions and dose per fraction. We will uncover the complexity of biological processes such as adscopal/bystander effects, tumor repopulation between fractions and reoxygenation of hypoxic tumors that are induced in the context of fractionated radiotherapy but cannot be explained by the BED model.

SPECIAL TECHNIQUES AND EQUIPMENT

Murine tumor models, small animal image-guided radiation therapy research platform, sensitive hypoxia reporter system, immunohistochemistry