PROJECT 1

DoS: **Antonella Castellano**

Title: **Decoding glioma molecular phenotypes by advanced radiomic and radiogenomic analyses**

Curriculum: Experimental and Clinical Medicine

Residency Program: Radiodiagnostica

Link to OSR/UniSR personal page:
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Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

Neuro-oncology is quickly moving beyond traditional histopathological diagnosis to molecular stratification of brain tumors. Indeed, several studies over the past two decades have identified both focal and genome-wide markers to help classify gliomas in the clinic and to divide them into biologically discrete subgroups. This trend is reflected by the new 2016 WHO classification of brain tumors which, for the first time, uses molecular parameters in addition to histology for tumor diagnosis.

Understanding how these molecular phenotypes are reflected in noninvasive imaging is crucial to define novel MRI biomarkers that can be used as surrogates for tissue-based molecular subtyping required to predict prognosis, to develop individualized patient therapies and to follow-up patients. Advanced MRI (aMRI) techniques such as diffusion MRI (dMRI) and perfusion-weighted imaging (PWI) add important structural, physiological and hemodynamic information to measure biological properties quantitatively and non-invasively. Radiomics is an emerging field of imaging that extract quantitative data from MR images and represents the basis of radiogenomics, a new discipline aiming at determining the association between parameters extracted from large-scale radiomic analysis, genomic signatures and molecular phenotypes of gliomas or clinical endpoints, resulting in both prognostic and predictive models. Radiomics circumvents the histological limit of partial availability of tissue sample by assessing the comprehensive three-dimensional tumor bulk by means of imaging information. Moreover, as radiomic biomarkers can be applied both at initial presentation and during disease follow-up, they can give a panoramic view of tumor molecular spatial heterogeneity, and possibly assess dynamic changes of molecular profiles over time (temporal heterogeneity).

To date, it remains largely unclear how advanced radiomic features relate to glioma molecular phenotypes. As such, this project aims at evaluating if noninvasive radiomic biomarkers can be exploited to determine the tumor molecular status. To this end:

1. a quantitative radiomic analysis will be performed on MRI data of a retrospective, discovery cohort of glioma patients (including conventional MRI, diffusion MRI and PWI data) that had undergone surgical resection, in order to search for the association between quantitative radiomic biomarkers (including 1st-order, volume, shape, texture features) and pathological, molecular and clinical findings by means of radiogenomic approaches;
2. a prospective, validation cohort of glioma patients will be investigated, in order to exploit the potential of radiomic to predict glioma molecular patterns and patients' clinical outcome.

In Task 1, selected glioma patients, whose diagnosis had been performed according to WHO 2016 classification, will be included in the discovery cohort. A molecular panel targeting multiple genes involved in glioma metabolism and proliferation will be set on tumor samples, including mutant IDH1 and ATRX for lower-grade gliomas as well as primary and secondary GBM, and other genes such as CDKN2A, EGFR, PTEN, PDGFRA, TP53, CDK4, NF1, CDK6 for glioma subtyping. Clinical parameters such as progression free survival (PFS) and overall survival (OS, when available) will be recorded too. Radiomics features will be correlated to molecular and clinical parameters using statistical methods, in order to search for radiogenomic descriptors of glioma molecular and clinical subtypes. In Task 2, these radiogenomic biomarkers will be validated in a prospective cohort of glioma patients, that will be recruited troughout all the duration of the PhD project.

Skills to be acquired by the student:

The Physician Scientist recruited to this project will be in charge of the analysis of advanced MRI data in Task 1, and of the acquisition and analysis of MRI data in Task 2. He/she will acquire experience in using clinical and advanced analysis softwares for image processing such as Olea Sphere, LIFEx software, Python and Matlab toolkits.

References (max. 3)

1. A. Castellano, A. Falini, Progress in neuro-imaging of brain tumors. *Curr Opin Oncol* **28**, 484-493 (2016).
2. S. Abrol, A. Kotrotsou, A. Salem, P. O. Zinn, R. R. Colen, Radiomic Phenotyping in Brain Cancer to Unravel Hidden Information in Medical Images. *Top Magn Reson Imaging* **26**, 43-53 (2017).
3. D. N. Louis *et al.*, The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* **131**, 803-820 (2016).