PROJECT 1

DoS: Alberto Briganti

Title: Development of a Novel Signature Integrating Clinical, Imaging And Epigenetic Information to Tailor Pelvic Nodal Treatment in Prostate Cancer

Curriculum: Experimental and Clinical Medicine

Residency Program: Urology

Link to OSR/UniSR personal page: http://research.hsr.it/en/institutes/urological-research-institute/alberto-briganti.html

Project description (*Number of characters*, *including spaces*: 2.948):

The presence of Lymph Nodal Invasion (LNI) is an adverse prognostic factor associated with higher recurrence rates and decreased long-term survival in prostate cancer patients (PCa). Efforts should be made to improve prediction of LNI in men suitable for surgical intervention. Our hypothesis is that lymphatic spread of PCa cells can be predicted through integration of clinical variables, radiologic and epigenomic information. Recent evidences demonstrated that multi-parametric MRI (mpMRI) and DNA methylation features may improve patient stratification to identify men at risk of LNI (1,2).

Specific Aim 1:
To identify the index lesion and to assess the pre-operative clinical stage using mp-MRI. Data regarding clinical stage (namely, tumour T stage and tumour volume at mp-MRI) will be included into a predictive model. Moreover, the index lesion(s) identified at mp-MRI will be targeted at the time of prostate biopsy.
Specific Aim 2:
To validate the recently published DNA-methylation signature, consisting of 25 DNA methylation probes, to predict the lymph-node invasion.
Specific Aim 3:
To integrate clinico-pathological characteristics with data from mp-MRI and DNA-methylation signature for the prediction of LNI.

Experimental Design Aim 1:
Prospective study enrolling patients diagnosed with targeted + systematic biopsy and treated with RP and PLND. Prostate biopsy will be performed in case of positive mp-MRI. Indication to prostate biopsy will be considered when PI-RADS score ≧3. These patients will undergo systematic sextant biopsy plus MRI-targeted biopsy.
Experimental Design Aim 2:
The epigenetic signature will be tested on DNA extracted from PCa tissue obtained at prostate biopsy. In particular, the epigenetic score will be calculated on the prostatic tissue using the epigenetic signatures based on the following reference genes: NXPH2, NCAPH, TRIB1, PCDHA1-PCDHA8, C3orf37, C9orf3, PCDHA1-PCDHA8, CPN1, TCF7L2, ROBO1, GFPT2, FBXO47, SKI, HDAC9, CARS, SLC6A17, BCAT1, GAS1, RAI1.
In patients diagnosed with PCa who will be treated with RP, ePLND will be performed when the predicted LNI risk will exceed 7% according to the new Briganti Nomogram (3). In patients who will be affected by pN1 disease, the positive lymph node with the maximum diameter will be submitted to methylation analysis. The results of epigenetic analysis from the positive node will be compared to the positive cores of both index lesion and systematic biopsy for epigenetic profile in each patient.

Experimental Design Aim 3:
All patients will have available information from clinical data, histo-pathological data, pre-operative mp-MRI, and epigenomic analysis. These data will be used to develop a novel predictive model assessing the risk of LNI.

Skills to be acquired by the student:

The PhD student will help to coordinate the project and will be responsible of patient enrolment, data acquisition, data analysis and widespread dissemination of the results of the project. Our project will provide skills in biological research and laboratory practice.
At the end of the project, the student will have an expertise on the following tools Illumina array Infinium MethylationEPIC BeadChip, GeneRead FFPE kit (Qiagen), Minfi Bioconductor package.
The student will develop more general practical and technical skills such as:
-analysis and interpretation of masses of scientific data
-logical thinking, numeracy and computing skills
-awareness of current issues and ethical debates
-communication skills including report writing and making presentations
-team work and strong interpersonal skills.

References (max. 3)

(1) Brembilla et al. European Radiology 2018. May;28(5):1969-1976.
(2) Mundbjerg et al. Genome Biology. 2017. Jan 12;18(1):3
(3) Gandaglia G. et al. European Urology. 2019 Mar;75(3):506-514.