PROJECT

Supervisor:	Alberto Briganti
Title:	Biological Pathways and Next-Generation Imaging Features Predicting Prostate Cancer Progression in Active Surveillance
Curriculum:	Molecular Medicine; Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	https://www.hsr.it/dottori/alberto-briganti

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Active surveillance (AS) is a treatment option for low-risk localized Prostate Cancer (PCa) patients aiming to avoid unnecessary side effects in those not requiring immediate treatment. Radical treatments are given if the disease progresses to a life-threatening condition. Approximately 30% of AS patients experience upgrading within 1 year, with more than 60% receiving definitive treatments at 10 years [1,2]. Available tools predicting reclassification are characterized by poor performance characteristics and biomarkers are still lacking. Genomic alterations in DNA repair genes (e.g., BRCA1/2 and ATM) have been associated with an aggressive phenotype [3]. Heterogeneity in PCa cell gene expression and the interplay with tumor microenvironment might be crucial in disease progression [4]. Spatial transcriptomic analysis might reveal context-dependent gene expression changes. Moreover, increased expression of Prostate-Specific Membrane Antigen (PSMA) has been linked with PCa aggressiveness, and imaging biomarkers based on PSMA PET/MRI have been correlated with high-grade or locally advanced disease [5].

Rationale and hypothesis

By characterizing low-risk PCa using molecular biology and imaging at diagnosis, we can identify mechanisms responsible for aggressiveness and improve the selection of AS candidates. The combination of novel biomarkers identified through an in-depth assessment of biological pathways associated with progression and next-generation imaging features could help characterizing the landscape of PCa and tailor individualized treatment strategies.

Objectives and specific aims

1. Develop and validate a novel model combining clinical features with somatic mutations, PSMA-PET quantitative parameters, and PSMA expression at IHC to identify patients who will experience upgrading at 1-year follow-up
2. Assess the impact of genetic heterogeneity on the risk of upgrading

3. Explore the role of gene expression patterns, spatial arrangement of cell populations, and microenvironmental features in PCa progression

4. Investigate the role of PSMA PET imaging in identifying AS patients who will progress

Expected outcomes

The in-depth characterization of biological and next-generation imaging features associated with upgrading will lead to the development of a tool to select AS candidates which might improve oncologic control by treating men at higher risk of progression upfront, enable personalized decisions, and reduce healthcare costs and de-intensify follow-up procedures for those with indolent disease. This would streamline the current AS diagnostic pathway and reduce associated costs and side effects. The availability of reliable tools to identify patients at higher risk of progression would increase the adoption of AS, thereby reducing the risk of overtreatment. This would reduce the burden of low-risk PCa and result in substantial savings for healthcare systems.

Skills that the student should acquire (max. 600 characters including spaces):

The student should acquire skills in data collection and analysis using AI algorithms to enhance predictive models. They will gain experience in patient enrollment and management, as well as in performing immunohistochemistry, spatial transcriptomics, and tissue collection. The student will also develop expertise in evaluating PSMA PET and MRI images, planning study visits and procedures, and presenting research at international conferences. Additionally, they will learn to submit data for publication in peer-reviewed journals and to answer to reviewers' comments.

References (max. 15)

[1] Timilshina N et al. Long-term Outcomes Following Active Surveillance of Low-grade Prostate Cancer: A Population-based Study Using a Landmark Approach. J Urol 2023;209:540-548.

[2] Leni R et al. Is Active Surveillance an Option for the Management of Men with Low-grade Prostate Cancer and a Positive Family History? Results from a Large, Single-institution Series. Eur Urol Oncol 2023;6:493-500.

[3] Carter HB et al. Germline Mutations in ATM and BRCA1/2 Are Associated with Grade Reclassification in Men on Active Surveillance for Prostate Cancer. Eur Urol 2019;75:743–9.

[4] Hirz T, et al. Dissecting the immune suppressive human prostate tumor microenvironment via integrated single-cell and spatial transcriptomic analyses. Nat Commun 2023;14(1):663.

[5] Emmett L et al. The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study. Eur Urol 2021;80:682–9.