

	PROPOSAL AS DIRECTOR OF STUDIES & RESEARCH PROJECT FOR PHYSICIAN-SCIENTIST POSITION	MO-PHDMM-1a Rev. 02 del 21/05/2019
		Page 3 di 4

PROJECT 1

DoS: FRANCESCO MONTORSI

Title: A novel comprehensive and imaging-guided approach to optimize the detection of lymph node metastases in prostate cancer

Curriculum: Experimental and Clinical Medicine

Residency Program: UROLOGY

Link to OSR/UniSR personal page: <https://www.hsr.it/dottori/francesco-montorsi>

Project description (Number of characters, including spaces: 3214):

The presence of lymph node invasion (LNI) is an adverse prognostic factor associated with higher recurrence rates and decreased long-term survival in prostate cancer (PCa) (1). A correct nodal staging plays a key role in the identification of high-risk patients with poor prognosis who would benefit from additional therapies. Moreover, extended pelvic lymph node dissection (ePLND) represents a therapeutic approach in some patients. Conventional and novel imaging modalities have relatively poor performances in nodal staging before surgery. For these reasons, an ePLND still represents the optimal method to detect LNI and it is currently recommended in patients with an LNI risk higher than 5% according to the Briganti nomogram. Although these models have good accuracy, the use of arbitrary cut-offs for the selection of candidates for ePLND is associated with a substantial risk of both unnecessary procedures and undetected metastases (2). A role for radio-guided surgery has been recently proposed in PCa using PSMA as target tracer (3). PSMA represents a cell surface protein that is highly overexpressed on most PCa tumour cells and it is used to target PCa tumor cells. In this project, radioactive labelling of PSMA ligands with gamma-emitting radionuclides (99mTechnetium-PSMA-I&S) will be used for intraoperative surgical guidance with gamma probes based on acoustic and visual feedback. The experimental plan comprises several steps. First, we will evaluate the sensitivity, specificity and overall accuracy of 99mTc-PSMA-RGS in the detection of lymph node metastases by comparing PSMA and intraoperative findings with final pathology (namely, presence of LNI) using a template-based analysis in 100 consecutive patients with localized prostate cancer undergoing robot assisted radical prostatectomy. The PhD student will be fully involved in all surgical steps and will perform – in collaboration with the Pathology Department- different immunohistochemical analyses for radioactive-positive and -negative LN lesions (PSA, P501S, PSMA, NKX3.1, and pPSA). Moreover, he/she will perform DNA extraction of LN metastasis and will be involved in data interpretation and analyses of next-generation sequencing which will be performed to determine differential gene expression between radioactive-positive and -negative lesions. Finally, we also hypothesize that the detection of circulating prostate cancer cells before surgery could help patient' stratification and might represent an independent prognostic factor of LNI. The PhD student will collect and assess the absolute number of circulating prostate cancer cells determined by gating on PSA, PSMA, CK, CD45 using flow cytometric analysis prior to surgery.

The aim of our study is to improve preoperative LNI stratification in patients at high risk of LNI by integrating clinical, radiologic, immunohistochemical, and flow cytometric data to better identify patients suitable for ePLND and to optimize the diagnosis of nodal metastases and reduce the number of unnecessary lymph node dissections.

In this research project, the PhD student will address the following aims:

- To assess the diagnostic accuracy of 99mTc-PSMA-RGS in the identification of LNI in men at higher risk for nodal involvement;

- To evaluate and calculate the number of circulating prostate cancer cells by flow cytometric analysis in these patients;
- To compare the genomic profile of 99mTechnetium-PSMA-positive and negative lesions;
- To develop novel prediction models stratifying men who will or will not benefit from extended pelvic lymphadenectomy by integrating advanced imaging, histopathological and cytofluorimetric markers.

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.

The student will improve fundamental technical skills such as:

- unique experience in radio-guided surgery in PCa
- analysis and interpretation of genomic data
- immunohistochemical and cytofluorimetric analysis
- development of prognostic, multivariable models
- communication skills including report writing and presentations
- team work and strong interpersonal skills.

References (max. 3)

1. Abdollah F, et al. J Clin Oncol. 2014; 10;32(35):3939-47.
2. Fossati N, et al. European urology. 2017;72(1):84-109.
3. Maurer T, et al. European urology. 2019; 75(4):659-666.