**PROJECT**

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| **Supervisor:** | Paolo Giorgio Arcidiacono |
| Title: | **"Decoding the biological, molecular and clinical determinants of long-term efficacy of Gastric Outlet Restoration in Pancreatic Cancer"** |
| *Curriculum:* | Experimental and Clinical Medicine |
| Link to the personal page of the University or relevant hospital site website: | __ https://www.unisr.it/docenti/a/arcidiacono-paolo-giorgio |

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

**Background/gap of knowledge**

The incidence of pancreatic cancer (PDAC) is constantly increasing (1-2). Nutritional deterioration is a key yet underestimated issue in PDAC patients. Anorexia, weight loss, malabsorption, and cachexia, negatively impact treatment response and overall survival (3). Additionally, 10–20% of patients develop a tumor-related gastric outlet obstruction (GOO), further worsening nutritional status.

in recent years, Endoscopic Ultrasound (EUS) is leading the possibility of handling cancer-related GOO. More specifically, EUS-guided gastroenterostomy (EUS-GE) using lumen-apposing metal stents (LAMS) creates a surgical-range anastomosis to bypass the obstruction with minimal invasiveness and low rate of recurrences (4-5).

Given these benefits, EUS-GE is now also applied to selected benign conditions (e.g., chronic pancreatitis, gastroparesis). (6-7)

However, while short-term outcomes are promising, long-term durability remains unclear. Peri-prosthetic tissue reactions such as ingrowth/overgrowth may compromise stent function, yet the mechanisms and risk factors are not well understood.

Beyond mechanical relief, nutritional recovery likely depends on complex interactions among tumor biology, patient-specific factors (e.g., enzyme replacement, inflammation), and host-device responses. For example, molecular subtypes of pancreatic cancer may influence metabolism and therapy response, shaping nutritional trajectories.

A deeper understanding of these multidimensional factors is needed to optimize care, predict outcomes, and personalize strategies.

**Rationale and hypothesis**

We hypothesize that nutritional recovery and long-term EUS-GE success are influenced by tumor subtype, patient characteristics, pharmacologic therapies and host–stent interactions.

**Objectives and specific aims**

To prospectively evaluate clinical, biochemical, radiological, functional and molecular data, to identify the factors involved in nutritional outcomes and procedure durability after EUS-GE in pancreatic cancer patients.

Specific aims:

- Assess post-procedural nutritional recovery (e.g., BMI, biochemical and morphological data) and correlate with tumor subtype, molecular profile, motility, inflammation and exocrine function / supplementation.

- Investigate long-term EUS-GE outcomes, including stent patency, tissue response [hyperplasia, fibrosis, ingrowth, overgwrowth], GOO recurrence, and re-intervention needs.

- Use Artificial Intelligence (AI) algorithms to integrate clinical/imaging/molecular data and define predictive profiles for procedural durability.

**Expected outcomes**

- Define predictors of nutritional improvement in patients with pancreatic cancer undergoing GOO restoration

- Characterize long-term stent function and tissue responses, exploring host or tumour-related factors associated with adverse LAMS reactions to speculate preventive measures.

- Support strategies for personalized pancreatic nutritional care and enzyme replacement therapy based on disease and patient-specific factors.

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

o Advanced knowledge of pancreatic cancer pathophysiology and molecular classification

o In-depth knowledge of endoscopic management of GOO

o Knowledge of molecular pathways regulating inflammation and healing in gastrointestinal tissues.

o Collection and management of clinical data (biobanking, data curation)

o Ability to interpret and correlate clinical, biological (including transcriptomic) and morphological (including body composition) data with clinical outcomes, including incorporation of Artificial Intelligence.

**References** (max. 15)

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2. .McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846-4861. doi:10.3748/wjg.v24.i43.4846.

3. Heckler M, Klaiber U, Hüttner FJ, Haller S, Hank T, Nienhüser H, Knebel P, Diener MK, Hackert T, Büchler MW, Probst P. Prospective trial to evaluate the prognostic value of different nutritional assessment scores for survival in pancreatic ductal adenocarcinoma (NURIMAS Pancreas SURVIVAL). J Cachexia Sarcopenia Muscle. 2021 Dec;12(6):1940-1947. doi: 10.1002/jcsm.12796. Epub 2021 Sep 20. PMID: 34545696; PMCID: PMC8718045.

4. Liu C, An L, Zhang S, Deng S, Wang N, Tang H. Association between preoperative sarcopenia and prognosis of pancreatic cancer after curative-intent surgery: a updated systematic review and meta-analysis. World J Surg Oncol. 2024 Jan 30;22(1):38. doi: 10.1186/s12957-024-03310-y. PMID: 38287345; PMCID: PMC10825983.

5. McCarty TR, Garg R, Thompson CC, Rustagi T. Efficacy and safety of EUS-guided gastroenterostomy for benign and malignant gastric outlet obstruction: a systematic review and meta-analysis. Endosc Int Open. 2019 Nov;7(11):E1474-E1482. doi: 10.1055/a-0996-8178. Epub 2019 Oct 23. PMID: 31673620; PMCID: PMC6811354.

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7. Teoh AYB, Lakhtakia S, Tarantino I, Perez-Miranda M, Kunda R, Maluf-Filho F, Dhir V, Basha J, Chan SM, Ligresti D, Ma MTW, de la Serna-Higuera C, Yip HC, Ng EKW, Chiu PWY, Itoi T. Endoscopic

ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): a multicentre randomised controlled trial. Lancet Gastroenterol Hepatol. 2024 Feb;9(2):124-132. doi: 10.1016/S2468-1253(23)00242-X. Epub 2023 Dec 4. PMID: 38061378.