

Abstract

Adenocarcinoma of the gastroesophageal junction (GEJ) and stomach are among the most common malignancies and causes of cancer death worldwide, including Portugal which has one of the highest incidence rates in Europe, predominantly occurring in patients > 65 years of age [1]. In patients with locally advanced disease, perioperative chemotherapy (PCT) is considered standard of care, as different clinical trials demonstrated its superiority in improving survival, when compared to surgery alone [2]. However, PCT is not free of adverse effects, promoting significant physiological deterioration [2], which is a major risk factor for poor postoperative outcomes [3]. Even with the most recent PCT regimes, around 50-60% of patients develop postoperative complications [2], which limits surgical and survival outcomes [3]. Given the growing incidence of proximal gastric cancer and GEJ tumors and because these patients often present with age-related functional decline, comorbidities and geriatric syndromes, these patients are at greater risk for adverse outcomes [4].

Currently, PROTECT team is working with machine learning to optimize surgical risk prediction and identify patients that need to be optimized before proceeding to surgery (in the scope of DSAIPA/DS/0042/2018). Ultimately, our vision is to enhance the clinical approach to those signaled as high-risk patients, providing safe and effective treatment options in a more patient-centered fashion. PROTECT team will contribute to this vision by exploring the utility of prehabilitation. Prehabilitation is an intervention designed to enhance physiological reserve before exposure to surgery [5]. A recent meta-analysis supports its role in attenuating postoperative complications in cancer patients submitted to major surgery [6]. However, existing studies show a clear bias towards certain types of cancers (esophageal, colorectal) and are underpowered to address major outcomes like postoperative complications. To understand if these benefits can be transferred to other cancer settings, PROTECT team will perform a randomized controlled trial. Patients with locally advanced, potentially resectable gastric or GEJ adenocarcinoma, undergoing PCT with FLOT regimen will be recruited at IPO-Porto and randomized (1:1 ratio) to control (CONT; usual care with medical optimization, nutritional and psychological care) or prehabilitation (PREHAB, usual care + home-based exercise training program) groups. Exercise intervention will comprise aerobic and resistance training plus inspiratory muscle training [6]. The primary outcome is reduction in postoperative complications and secondary outcomes will be enhancement in treatment, health and survival-related outcomes, patient-reported outcomes, and healthcare resource utilization.

Emerging evidences suggest that many negative effects of major surgery can be reduced by attenuating surgical stress [7]. Whether prehabilitation modulates the magnitude of surgical-stress response, and if a lower response is proportional to better postoperative outcomes is unknown. PROTECT team will explore these questions by collecting hemodynamic data and body fluids (blood and urine, before, immediately after, 24h and 48h after surgery). Plasma samples will be used to characterize endocrine, metabolic, cardiovascular and immune response to surgical stress, and urine samples for catabolic markers. By using multivariable analysis, we will integrate generated data with postoperative outcomes, envisioning identifying a risk profile that should guide preventive actions.

The impact of prehabilitation on tumor downstage will also be evaluated by PROTECT team to ascertain the potential benefits of PREHAB on tumor development and response to chemotherapy. Indeed, epidemiologic [8] and preclinical studies from our group [9, 10] and others [11] support the hypothesis that physical exercise has anti-tumor effects. Exercise seems to change tumor microenvironment, by normalizing microvasculature, hypoxia and metabolism, thus promoting competent cytotoxic immune cell infiltration [12]. Studies from mouse models also support that aerobic exercise increases tumor perfusion and drug delivery [13, 14]. Currently, it is unclear whether human tumors respond to exercise. Thus, slides of tumor section obtained before (biopsy) and after PCT (at time of resection) will be analyzed through immunohistochemistry to characterize proliferating index, apoptosis, vascular remodeling, hypoxia, endothelial adhesion molecules, immune cell penetration, metabolism, microsatellite stability, and glycosylation. Cells extracted from blood and fresh tumor tissue obtained at time of resection will also be prepared for immunophenotyping using flow cytometry. The validation of exercise benefits on tumor physiology, microenvironment, and on delivery and efficacy of chemotherapy will have a significant clinical impact, establishing exercise as an anti-cancer therapy.