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Università Vita-Salute
San Raffaele

APPLICATION TO ACT AS SUPERVISOR AND
RESEARCH PROJECT PROPOSAL

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21/02/2025

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PROJECT

Supervisor:

Prof. Ugo Elmore, MD PhD

Title:

Efficacy and feasibility of immunotherapy in combination with standard-of-care perioperative chemotherapy for patients with resectable esophageal adenocarcinoma

Curriculum:

Molecular Medicine - Experimental and clinical medicine

Link to the personal page of the University or relevant hospital site website:

<https://www.hsr.it/dottori/ugo-elmore>

<https://www.hsr.it/strutture/ospedale-san-raffaele/chirurgia-gastroenterologica>

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

Background/gap of knowledge

Esophageal cancer (EC) is the seventh leading cause of cancer-related mortality worldwide, with esophageal adenocarcinoma (EAC) representing the predominant subtype in the Western world due to the dramatically rising prevalence of obesity and gastroesophageal reflux disease (GERD). EAC treatment is multimodal and includes neoadjuvant chemoradiotherapy (CRT), perioperative chemotherapy (CT), and surgery. Immunotherapy utilizes immune checkpoint inhibitors (ICIs) which target programmed cell death protein-1 (PD-1) or its ligand-1 (PD-L1) to enhance tumor antigen release, increase tumor-infiltrating lymphocytes, and stimulate an immune response. Current international guidelines recommend immunotherapy with nivolumab or pembrolizumab for metastatic or locally advanced non-resectable cancers, particularly when neoplastic cells exhibit deficient mismatch repair with microsatellite instability-high (dMMR/MSI-H), PD-L1 overexpression (defined by a combined positive score [CPS]>1), or human epidermal growth factor receptor 2 (HER-2) amplification. Nivolumab is also the only approved ICI as adjuvant therapy for patients with esophageal or esophagogastric junction (EGJ) cancer after neoadjuvant CRT and radical surgical resection without pathologic complete response (pCR). Finally, the MATTERHORN trial has recently demonstrated a clinically meaningful improvement in event-free survival (EFS) for patients with resectable, locally advanced gastric and EGJ tumors treated with perioperative ICIs in addition to the standard-of-care CT. However, to date, no immunotherapy regimens have been approved for patients with locally advanced, resectable EAC receiving perioperative CT.

Rationale and hypothesis



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Our hypothesis is that patients with locally advanced, resectable EAC may benefit from the addition of an ICI to standard-of-care perioperative chemotherapy. The rationale is that the proportion of patients achieving pCR with traditional protocols is very low (16%), and immunotherapy could enhance the immune response, reduce the number of viable tumor cells, and decrease the likelihood of recurrence after surgery.

Objectives and specific aims

The main aims of the present project are:

- 1) to demonstrate that the addition of immunotherapy to perioperative CT in patients with locally advanced, resectable EAC increases the rate of pCR and major pathologic response (MPR)
- 2) to determine how immunotherapy affects the intraoperative and postoperative outcomes, particularly morbidity, mortality, and the rate of R0 resection
- 3) to evaluate whether immunotherapy is well tolerated and its effect on surgical attrition
- 4) to assess the effect of immunotherapy on biomarker expression other than the exclusive CPS score, which could potentially differentiate individual characteristics of response-to-therapy

Expected outcomes

We expect that perioperative ICI will significantly improve pCR and MPR, ultimately leading to a reduction in postoperative recurrence and an increased survival. Based on available safety data of immunotherapy in the postoperative setting and other tumor types, we do not believe that ICI will negatively impact surgical outcomes compared with existing regimens.

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

The student will acquire comprehensive knowledge in the design, development, and execution of a clinical trial, including an understanding of trial methodologies, ethical considerations, and regulatory standards. The student will also develop strong analytical skills to critically assess clinical evidence and interpret results, applying statistical techniques to analyze data and draw meaningful conclusions. Additionally, the student will gain proficiency in scientific paper writing, learning to structure manuscripts and present findings clearly and effectively in both oral and written English.

References (max. 15)

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11. Wong LY, Liou DZ, Backhus LM, Lui NS, Shrager JB, Berry MF. The impact of neoadjuvant immunotherapy on perioperative outcomes and survival after esophagectomy for esophageal cancer. *JTCVS Open*. 2023;14: 547-560. doi: 10.1016/j.jxon.2023.03.015.
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