Title *Complete pathologic response rectal cancers EYSAC.1 Study*
Acronym CORSiCA

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Name of the PI's Host Institution for the project. *Fondazione Policlinico Unversitario A. Gemelli*
Name of Project Partner. European Society of Surgical Oncology - ESSO
Proposal duration. 36 months

Proposal Summary

Background. About 20% of rectal cancers who underwent neoadjuvant treatment (neoCHT-RT) achieve a pathological complete response in the surgical specimen (ypT0); however, about 10% of ypT0 present metastatic nodes (N+). ypT0N+ identification could be crucial in order to tailor treatments.
Aim 1. To create a large European Database of ypT0.
Aim 2. To compare ypT0N0 *vs* ypT0N+ with respect of their clinical/radiological/molecular features.
Aim 3. To investigate long term results.
Preliminary Study. Dr Lorenzon is the PI of an Italian retrospective multicentric study conducted on 230 ypT0 focused on treatment and outcomes.
Design. The PI will operate at Fondazione Policlinico Universitario A. Gemelli in partnership with the European Society of Surgical Oncology (ESSO). An DB will be used by ESSO-affiliated centres for collecting the clinical, pathological and radiological data of ypT0N0/N+, previously treated (last 5 years) and prospectively enrolled (6 months + 2 years of follow-up). ypT0N0 and ypT0N+ will be compared for the clinical/pathological variables. Uni-multivariate survival analyses (end-points: OS, DFS, DSS) will be conducted at 2 years of follow-up.
Impact. This is the first study aimed to investigate ypT0N+ features; their accurate identification could lead to treat safely thousands of ypT0N0/year with local excisions leaving major surgery for N+ patients. Results will change practice and reduce considerably health-related costs; moreover, the molecular profiles will open new frontiers of research.

Synopsis

Prospectus. The **COmplete pathologic ReSponse rectal Cancers EYSAC.1 Study (CORSiCA)** proposed by Dr Lorenzon will be conducted at *Fondazione Policlinico Unversitario A. Gemelli* of Rome in partnership with the European Society of Surgical Oncology (ESSO) – Young Alumni Club, and it will focus on rectal cancer patients who underwent neo-adjuvant treatment followed by surgical resection and had a final pathologic diagnosis of absence of residual viable tumoral cells within the rectal wall specimen (**pathologic complete response, pCR - ypT0**).

Rectal Cancer and Pathologic Complete Response. With about 135.000 new European (EU) cases[1-2] each year, rectal cancer is a major European issue representing also a field of major investigations. Indeed, over the last 3 decades important advances have been made in the clinical/surgical management of these patients: the most significant ones were the introduction of total mesorectal excision (TME)[3-4] and the use of neo-adjuvant (chemo)radiation treatments (neoCHT-RT)[5-9] which changed dramatically the state of art and the multimodal approach to this disease. Currently, the latest international guidelines recommend performing a neoCHT-RT in locally advanced, non-metastatic rectal cancers, clinically staged as ≥T3 any N, anyT N+ or if the circumferential resection margin (CRM) is less than 1 mm, since this approach results in less local recurrences, tumor down-sizing and down-staging[10-11]. In line with all the improvements made so far, the ultimate effect of neoCHT-RT is the achievement of a complete response, which may be defined as clinical (absence of residual primary tumor clinically detectable, cT0) or pathological. ypT0 occurs in about 20% of patients who underwent neoCHT-RT[12-13]. Of note, neoadjuvant treatment modalities include a short-course radiotherapy (short RT) followed by immediate surgery or a long course chemo-radiotherapy (CHT-RT) followed by surgery delayed after an interval of at least 4 weeks[10].

Literature and ypT0. Literature about complete responders is quite recent and started to emerge just over the last 15 years. Although very few large retrospective studies[13-17] or systematic reviews/meta-analyses[18-20] have been published so far, results are still at an early stage, mostly because there are no robust markers predictive of pCR (molecular, clinical or radiological)[19-20], a number of surgical approaches have been considered (from local excisions to abdominoperianel resection)[14] and there is no *consensus* regarding the adjuvant treatment following surgical resection[16]. However, the management of response following neoCHT-RT is the challenge of our times.

ypT0 N+ Rectal Cancers. A key issue in relation to pCR, is the presence of residual cancerous cells within lymph-nodes harvested in the surgical specimen (ypT0N+). These patients account for the 6.7-17.4%[13;21] of ypT0 and are seldom analyzed, since the vast majority of studies in this field has been conducted pooling together ypT0-ypT2 patients[21-22]; accordingly, a large analysis based exclusively on the ypT0 subgroup is still missing. Nevertheless, literature published so far documented that a clinical nodal positivity before neoCHT-RT has been correlated with nodal metastases[21-23]. An accurate prediction of the nodal *status,* however, would be crucial in order to tailor surgical choices.

Aims

- ✓ **Specific Aim 1.** To create a large Database of ypT0 patients from multiple institutions by involvement of young researchers (short-term aim)
- ✓ **Specific Aim 2.** To compare ypT0N0 *vs* ypT0N+ patients with respect of their clinical and molecular features (mid-term aim)
- ✓ **Specific Aim 3.** To define pattern and timing of relapses and to conduct a multivariate analysis of survivals which would include the N *status* and the use of adjuvant treatment (long-term aim)

Methods

Aim 1. Clinical data will be acquired using a Database (DB).

Aim 2. Patients presenting nodal positivity on TME specimens will be compared to the nodal negative patients for statistical purpose. Comparison will aim to define clinical and molecular features.

Aim 3. ypT0N0 patients and ypT0N+ patients will be compared with the end-points of overall survival (OS, any cause of death), disease free survival (DFS, first recurrence after surgical resection) and disease specific survival (DSS, death related to colorectal cancer) at 2 years of follow up.

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