Protocol code: REMNANT STUDY

SYNOPSIS

Title:	**REsection MargiNs After Neo-adjuvant Therapy for gastric cancer (REMNANT study)**
Sponsor:	Gruppo Italiano Ricerca Cancro Gastrico (GIRCG)
Coordinator	Daniele Marrelli
Rationale	Despite aggressive surgery, locally advanced gastric cancer (GC) is associated with poor prognosis even after potentially curative (R0) resection. In recent years, therapeutic approach to these forms changed remarkably in Europe, in light of the results of neo-adjuvant therapy trials. Nowadays, most European guidelines advice neo-adjuvant chemotherapy (NAC) in patients with cT2-T4 and/or cN-positive gastric cancer (1,2). Several studies demonstrated good response tumor rates in patients submitted to preoperative chemotherapy, with significant down-staging in most cases, and improved long-term outcome when compared with up-front surgery, above all when the triplet regimens (containing taxanes) are used (3,4). Anyway, surgical approach after NAC has been also reported to be potentially more complex than up-front surgery. In particular, the incidence of post-operative complications is not negligible, including anastomotic leaks above all when a total gastrectomy is performed (5, 6). It is evident that, when feasible, a subtotal gastrectomy should be preferred, provided that an adequate proximal resection margin is maintained. To date, no specific guidelines regarding surgical approach after NAC for locally advanced GC are reported, and surgical procedures are generally performed following the advices commonly used in up-front surgery (7). The GIRCG guidelines advice a minimum macroscopic proximal resection margin of 3 cm in advanced intestinal histotype, and 5 cm in the diffuse/poorly cohesive type (2). Anyway, it is unclear if these guidelines are also adequate after NAC, or if they should be adapted according to response to CHT, tumor location, tumor size, or other parameters. The aim of the present, retrospective multicentric study is to analyze the length of both proximal and distal macroscopic resection margins after NAC in potentially curative surgery for gastric cancer (R2 excluded). The relationship with microscopic involvement (primary end-point) and other secondary end-points will be also stratified according to a set of tumor-related and treatment related variables commonly used in clinical practice.
Clinical desing:	Observational, retrospective, multi-centre
List of partecipating	**TBD**

Centres	
Study design:	Data of patients with non-cardia gastric carcinoma treated with neo-adjuvant /perioperative chemotherapy (at least two cycles) will be retrospectively retrieved. R2 resections (macroscopic residual tumor) will be excluded. In patients with intra-operative diagnosis of positive resection margin, the relative distance will be considered for the analysis of primary end-point as a "positive event". The macroscopic resection margin will be evaluated on formalin-fixed specimen. A parallel prospective study for the correlation curve of fresh/formalin fixed specimen will start. The period of the study will be 2010-2021. Follow-up data will be collected, along with patient-related, tumor-related and treatment-related variables. The last follow-up date is established in December 2021.
Inclusion Criteria	Patients with primary, histologically confirmed non-cardia gastric carcinoma (Siewert type III is included) Absence of distant metastases (peritoneal, haematogenous, extra-regional lymph nodes) At least two cycles of preoperative CHT performed Potentially curative resective surgery (R0/R1) after treatment
Exclusion Criteria	Distant metastases Tumor involving the gastro-esophageal junction (Siewert I-II types) Macroscopic residual tumor (R2 resections)
End-points:	Primary: - incidence of microscopic positive resection margins (proximal, distant) Secondary: - Risk of anastomotic/duodenal stump recurrence - DFS - OS
Variables under study:	<u>Tumor-related:</u> Macroscopic proximal margin (cm) Macroscopic distal margin (cm) Clinical stage (8th edition) ypT (depth) ypN (no. of positive nodes) Longitudinal tumor location (Upper, middle, lower) Circumferential tumor location (lesser curvature, posterior wall, greater curvature, anterior wall) Maximum tumor size (cm) Regression grade (Becker) Lauren histotype WHO histotype LVI

	PNI Patient-related: Age Gender Treatment-related: CHT regimen (FLOT, DOC, EOX, ECF, others) No. of cycles Clinical response (PD, PR, SD) Lymphadenectomy (D1, D2, D2 plus) Extent of gastrectomy (partial, total) No. Removed nodes Combined resections
Study Objectives	Primary: Calculate the risk of positive resection margins according to the macroscopic distance Stratify such risk according to clinico-pathological variables Secondary: Calculate the risk of anastomotic/duodenal stump recurrence according to the macroscopic margin positivity/distance Calculate DFS and OS according to such variables
Follow-up	As commonly performed in other studies. The diagnosis of anastomotic/duodenal stump recurrence will be based on endoscopic/bioptic diagnosis or imaging when these are not feasible.
Statistical methods	**Statistical analysis** Data exploration and coding will be performed according to standard criteria, as described in previous studies. The risk of positive resection margins according to macroscopic distance as well as other clinico-pathological variables will be evaluated by Mann-Whitney U-test or chi-square test, when indicated. Multivariate analysis of potential predictors of R+ margins will be performed by logistic regression. The risk of anastomotic-duodenal stump recurrence will be evaluated by Kaplan-Meier method (one-minus survival). The Cox proportional hazard model will be used for the analysis of predictors of DFS and OS. **Sample size** The hypothesis is that a sample size of at least 300 patients is necessary to perform the analysis
Duration of the Study	Nine months (six months for data retrieval, three months for statistical analysis)

Ethical Committee	NA
Data management	Scientific Secretary of the GIRCG
Deadline invio dati	15/12/2022

References:

1) Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(suppl 5):v38-v49.
2) De Manzoni G, Marrelli D, Baiocchi GL, Morgagni P, Saragoni L, Degiuli M, et al. The Italian Research Group for Gastric Cancer (GIRCG) guidelines for gastric cancer staging and treatment: 2015. Gastric Cancer. 2017 Jan;20(1):20-30.
3) Sugawara K, Kawaguchi Y, Seto Y, Vauthey JN. Multidisciplinary treatment strategy for locally advanced gastric cancer: A systematic review. Surg Oncol. 2021 Sep;38:101599.
4) Moore JL, Kumar S, Santaolalla A, Patel PH, Kapiris M, Van Hemelrijck M, et al. Effect of peri-operative chemotherapy regimen on survival in the treatment of locally advanced oesophago-gastric adenocarcinoma - A comparison of the FLOT and 'MAGIC' regimens. Eur J Cancer. 2022 Mar;163:180-188.
5) Claassen YHM, Hartgrink HH, Dikken JL, de Steur WO, van Sandick JW, van Grieken NCT, et al. Surgical morbidity and mortality after neoadjuvant chemotherapy in the CRITICS gastric cancer trial. Eur J Surg Oncol. 2018 May;44(5):613-619.
6) Bracale U, Corcione F, Pignata G, Andreuccetti J, Dolce P, Boni L, et al. Impact of neoadjuvant therapy followed by laparoscopic radical gastrectomy with D2 lymph node dissection in Western population: A multi-institutional propensity score-matched study. J Surg Oncol. 2021 Dec;124(8):1338-1346.
7) Marrelli D, Polom K, de Manzoni G, Morgagni P, Baiocchi GL, Roviello F. Multimodal treatment of gastric cancer in the west: Where are we going? World J Gastroenterol. 2015 Jul 14;21(26):7954-69.