

Factors affecting the survival of clinical T4b gastric cancer in the era of multimodal treatment: Italian locally Advanced Gastric cancer study (ITAGA Study) A nationwide multicentre retrospective study of the Italian Research Group for Gastric Cancer (GIRCG).

Numero di protocollo:	ITAGA STUDY
Numero di Versione del Protocollo:	ITAGA STUDY. 01
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1. INTRODUCTION

Worldwide, gastric cancer represents the fifth most common type of cancer and the sixth leading cause of cancer-related deaths. ¹

Despite a significant number of diagnosis in patients from Western countries are made at TNM stage III and IV, to date the adequate surgical treatment of locally advanced gastric cancer is still under debate.

Although surgical resection is currently considered as the best approach for realizing a curative (R0) treatment, despite few successful reports ^{2,3,4,5,6} of improved survival after extensive surgery, it is still discussed whether a multiorgan resection in case of T4b gastric cancer is really able to increase patients' survival due to a high rate of perioperative morbidity and mortality.

In this new era of neoadjuvant/perioperative treatment it is important to describe the adequate strategy for cT4b disease, defined through preoperative workup (mostly CT scan and possibly staging laparoscopy). Which is the rate of complete/partial response to multimodal treatment in locally far advanced disease? Should these patients be provided with the same extended multivisceral surgical approach adopted for non-responding patients? How these new treatment modalities have changed patients' prognosis.?

All these questions will be addressed in this retrospective study in which cT4b gastric cancer submitted to surgical resection with curative intent, with or without neoadjuvant treatment, will be analyzed to evaluate the response to pre/perioperative treatment, the

feasibility, safety and efficacy of multivisceral resection and its, surgical outcomes and finally short-, mid- and long-term overall and disease free survival (considering a 5-year follow up). The main objective of the study is to assess if neoadjuvant chemotherapy provided in this last decade to far advanced disease significantly reduced the rate of extended multiorgan resection requested to treat patients and positively affected postoperative outcomes and survival.

This is a nationwide multicenter retrospective study conducted on behalf of the Italian Research Group for Gastric Cancer (GIRCG).

2. BACKGROUND

Despite a decreased incidence of gastric cancer recently registered all over the world, every year there are 140.000 new diagnoses in Europe with 100.000 deaths.

Gastric cancer is the fifth tumor in the world for incidence with a diagnosis most often reached only at advanced stages ⁷. More specifically, according to the 8th Edition of the AJCC staging manual ⁸ of the stomach, T4b is defined as a “Tumor that invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum”⁹. The 8th AJCC staging system includes T4b Gastric Cancer in stage IIIA when nodal stage is defined as N0, in stage IIIB when nodal stage is defined as N1 or N2 and in stage IIIC if nodal stage is N3a or N3b. In a recent validation study of the 8th Edition of the AJCC TNM Staging System for Gastric Cancer using the USA National Cancer Database, analyzing 12.041 surgically resected gastric adenocarcinomas, 5-years survival rates were 30.5 % for stage IIIA, 20.1 % for IIIB and 8.3% for stage IIIC ⁸.

R0 surgery is the main goal of a curative treatment, requiring a combined resection of the organs involved by tumor ^{10,11}. Not all of the surgeons agree with a multivisceral resection (MVR) in case of T4b gastric cancer. It is reported to increase the overall survival but at the cost of negatively affecting perioperative morbidity and mortality.

Therefore, when analyzing the indication to MVR, the increased risk of postoperative complications and mortality must be considered despite the evidence that few patients may benefit from extensive resections ^{3,5}.

Different international guidelines point out that a systematic splenectomy is not necessary unless the tumor is located in the greater curvature of the upper stomach or in case of direct invasion of the spleen or the splenic hilum ^{12,13}, because it does contribute to increase perioperative morbidity without improving life expectancy. Moreover significant differences in term of 5-year survival between patients submitted to gastrectomy alone compared to patients who received gastrectomy associated to splenectomy or pancreatosplenectomy have not been reported ¹⁴.

In 2012 a retrospective Italian study analyzed the outcomes of patients with locally advanced gastric tumors submitted to extensive surgical resections ²: patients undergoing multiorgan resection did not show statistically significant differences on postoperative morbidity and mortality rates compared to palliative surgery and resective surgery without multiorgan resection

In the last decade, a multimodal approach of GC has been suggested with the adoption of neoadjuvant (preoperative or perioperative) treatment (NAC) based on the reason that, at least theoretically, it may reduce tumor volume, improve the R0 resection rate and eliminate micro metastases. A recent study reported a high rate of complete/partial responses (44,7%) after perioperative treatment (Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (FLOT) as compared to upfront surgery followed by chemotherapy for patients with locally advanced gastric cancer.¹⁵. Therefore, most of cT4b tumors (those responding to perioperative treatment) could undergo standard gastrectomy without combined organs resections. Consequently the management of patients with clinical T4b gastric cancers has significantly changed nowadays

The aim of this study is to perform a nationwide multicentre retrospective study (on behalf of GIRCG) to assess the overall rate of clinical T4b gastric cancer in referral national centers and to investigate whether surgical treatment (extended multiorgan resections vs standard gastrectomy) and outcomes are changed after the recent introduction of perioperative treatment for advanced tumors

3. AIM OF THE STUDY

The aim of this study is to evaluate the overall rate of cT4b gastric cancer and the rate of those submitted to perioperative treatment among national referral centers; to assess the type of surgery performed (MVR vs. standard gastrectomy) and the outcomes (intraoperative and postoperative, complications, oncological outcomes and survival) in patients submitted or not submitted to perioperative treatment; lastly, to assess the feasibility, the safety and the efficacy of MVR.

Therefore, we want to analyze the impact of perioperative treatment on type of surgery performed (MVR vs. standard gastrectomy), length of stay (LOS), postoperative complications, anastomotic leakage, readmission rate within 30 days, reoperation rate within 30 days, postoperative mortality and 3-year overall and disease free survival

Second, we want to compare short-term and oncological outcomes together with survival of MVR and standard gastrectomy.

3. DESIGN OF THE STUDY

This is a nationwide multicentre retrospective study. Each consecutive patients with malignant tumor of the stomach, clinically staged as cT4b, submitted to surgery between January 2008 and February 2017 and meeting the inclusion/exclusion criteria will be registered into the trial.

5. SETTING OF THE STUDY

This is an Italian National multicentre retrospective study, coordinated by the department of Oncology of A.O.U. S. Luigi Gonzaga – Orbassano (TO).

Prof. Maurizio Degiuli is the Principal Investigator of this study. Statistical analysis will be conducted by the Statistics Unit of University of Torino, Dept of Oncology (Fulvio Ricceri, PhD).

6. TIMING

Data collection deadline: September 2020.

7. STUDY POPULATION

All consecutive patients selected by established inclusion and exclusion criteria will be included in this study.

Planned sample size: according to our preliminary statistical analysis, a minimum of 400 patients to achieve results statistically significant.

Inclusion criteria

- Gastric Adenocarcinoma,
- clinical stage T4b according to the 8th edition of the American Joint Committee on Cancer
- Age >18 years old.

Exclusion criteria

- Emergency surgery
- Peritoneal carcinomatosis
- Tumor cells in peritoneal washing
- Distant Metastasis at preoperative workup

8. ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is 5-year overall survival of cT4b gastric cancer patients with or without preoperative (neoadjuvant) chemotherapy

8.2 Secondary Endpoints

- The overall rate of cT4b
- The overall rate of cT4b undergoing preoperative (neoadjuvant) chemotherapy
- The overall rate of cT4b undergoing postoperative (adjuvant) chemotherapy
- 3-year overall survival of patients with or without preoperative (neoadjuvant) chemotherapy
- 3- and 5-year DFS of patients with or without preoperative (neoadjuvant) chemotherapy
- The rate and type of pathological response to NAC (partial, complete, stable disease, progression)
- The Rate of downstaging after neoadjuvant chemotherapy
- The rate of patients with NAC submitted to MVR
- The overall rate of cT4b GC submitted to MVR
- Length of stay (LOS)

- Short- term postoperative complications within 30 days
- Short-term mortality within 30 days
- Rate of anastomotic leaks
- Rate of readmission in hospital within 30 days
- Rate of reoperation within 30 days
- Time and type of recurrence

Variables considered in the study

The results obtained will be analyzed both overall and grouped according to specific variables:

- Demographic and clinical features

- Age
- Gender (Male/Female)
- BMI
- ASA
- ECOG
- Charlson comorbidity score
- Perioperative treatment
- Type of treatment

- Surgery

- Type of surgery/surgical procedure (total/subtotal gastrectomy)
- MVR vs standard gastrectomy
- Surgical intent (palliative/curative)
- Organs involved by gastric cancer (mesocolon, transverse colon, pancreas, spleen, other...)
- Organs resected
- Type of lymphadenectomy (D1/D2/D3)

- Pathology

- Tumor site
- Tumor size
- Cell differentiation (G1/G2/G3)
- pTNM stage
- Recist grade
- Type of response to NAC (P,C, SD, P)
- Lauren type (intestinal/diffuse/mixed)
- Borrmann type (I/II/III/IV)

- Post operative outcomes

- Surgical complications
- General complications
- Lengths of stay
- 30days mortality
- 30days readmission

- 30days reintervention
- Oncological outcomes
 - Completion of perioperative treatment
 - Adjuvant chemotherapy
 - 3- and 5-year disease free survival
 - 3- and 5-year overall survival

9. DATA MANAGING AND PRIVACY

Patients information will be anonymized and de-identified prior to analysis by an Excel file sent to all participants centers. Clinical data will be obtained from medical records, hospital informatics systems and prospective clinical databases.

Results will be the property of Università degli studi di Torino and of the researchers involved in the conduction of the multicentre project.

10. ETHICAL CONSIDERATIONS

This is a retrospective study. No clinical decision for all involved patients will be influenced by this analysis, with the full compliance with the principles of ethical conduct in human research.

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