The Impact of Frailty on the Postoperative Outcomes of Gastric Cancer Surgery (TOREGA)

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SUMMARY

Background. Gastric cancer is an important health care problem even though treatment advances, and it is diagnosed mainly in elderly. Surgery is the main treatment for gastric cancer and is associated with a high rate of postoperative complications and mortality, even higher in older patients. Chronological age seems not to be the main factor influencing the worse outcome of older patients, comorbidities and frailty have also been taken into account recently.

Methods. Participation in the study will be offered to all centers that are currently part of the Spanish EURECCA (EUropean REgistry of Cancer CAre) Esophagogastric Cancer Registry. The impact of the frailty on different outcome variables will be evaluated. The main outcome variable will be 90-day mortality after the intervention. Health-related quality of life (HRQoL) will also be evaluated.

Objective. The objective of the study is to value the impact of frailty on gastric cancer surgery outcomes therein the Spanish EURECCA Esophagogastric Cancer Registry.

Introduction

Gastric cancer is the fifth most frequent cancer and the third cause of death due to cancer. The increase in life expectancy cause it to be diagnosed more and more in elderly people, with an average age at diagnosis of 68 years in the West (1, 2).

Surgery is the main treatment for gastric cancer and is associated with a high rate of postoperative complications and mortality, which is even higher in elderly patients (data from the ACS-NSQIP between 2007 and 2013: 30-day severe morbidity from 16.3% in 80 years and 30-day mortality from 1.2% in 80 years) (3).

Generally, advanced chronological age is considered a negative prognostic factor for complications and hospital stay in major surgery (4). Age per se, however, seems to be responsible only in part for the increased risk of postoperative complications (5).

Greater risks seem to be associated with other factors such as comorbidities, so, in the preoperative evaluation, variables such as the Charlson comorbidity index have been introduced (6, 7). Another variable that has emerged recently for the estimation of perioperative risk is frailty (8), which is defined as "a medical syndrome with multiple causes and contributors that is characterized by a decrease in strength, endurance and physiological capacity, which increases the risk of the vulnerability of the individual and/or death" (9). Surgery is a major stress factor that can disrupt physiological homeostasis; therefore, frailty has a clinical significance when considering surgery in elderly patients (6).

There are two main ways to measure frailty: one by clinical definitions of a fragile phenotype (10) and another by frailty indexes that assess the accumulated deficits in multiple domains (11). Measures to assess frailty are numerous and this is a limitation when standardizing and comparing studies (12); among the most used there are the Fried criteria (10), the frailty index of the Canadian Study of Health and Aging (CSHA-FI) (13) and the modified frailty index of Velanovich (mFI: modified Frailty Index) (14).

Other indices widely used in the clinic are the Geriatric 8 (G8) (15), which is recommended above all in elderly patients with cancer (16) and the Groningen index (GFI: Groningen Frailty Indicator) (17). The prevalence of frailty in elderly patients (65 years or older) is highly variable, probably due to the diversity in the definitions of frailty (4.0-59.1% in community residences, 10.4-56.0% in patients who are candidates for elective surgery) (18, 19, 20). The prevalence of frailty increases in females and with age (being 15.7% in patients aged 80-84 years and 26.1% in patients older than 85 years) (18).

Frailty appears in several studies as a more important indicator than chronological age with respect to postoperative results (20, 21, 22, 23). There are evidences that relate frailty, evaluated with different indices, with the increase of postoperative complications, hospital stay, need of discharge to convalescence centers, health costs, short and long term mortality, after major surgery (12, 20, 22, 24, 25, 26, 27, 28, 29).

Therefore, it is important to identify fragile patients to implement prevention programs through global geriatric assessments (CGA Comprehensive Geriatric Assessment). Just by having more clinical attention for more fragile patients after major surgery there can be better results of short and long-term postoperative mortality (22). Likewise, as demonstrated in randomized clinical studies, prehabilitation and global geriatric assessment programs improve the results in terms of postoperative complications and hospital stay (30, 31, 32).

The CGA is an established method to evaluate and optimize the physical state, the psychological, functional and social problems in elderly patients in order to improve the results of the treatments. It implies an interdisciplinary evaluation of multiple domains, followed by planning for analysis, treatment, rehabilitation and long-term follow-up (33).

This allows, in the first place, to intervene before an operation, to increase the physiological reserve of a patient, especially with exercise and nutrition (34, 35). In addition, the therapeutic decision can be guided by adapting the surgical recommendations to the physiological capacity of the patient; second, the knowledge of the increased risk of complications and the possible need for transfer to institutions (especially in patients who live alone) prepares patients and their families for postoperative evolution (8).

The majority of studies published in the literature on the relationship between frailty and postoperative results are retrospective studies, which evaluate populations of patients undergoing major surgery and who, in general, analyze short-term results (30-day mortality) (12, 20, 22, 24, 25, 26, 27, 28, 29). None of these takes into account the impact of surgery on the quality of life of this group of patients. Among all these studies there is very little information about the influence of frailty in gastric cancer surgery. There is only one retrospective study that focuses only on gastric cancer surgery, using the Groningen index and revealing an increase in in-hospital mortality and serious complications (Clavien-Dindo complications score ≥ 3) in fragile patients (25). Objective

The aim of the present study is to assess the impact of frailty on the results of gastric cancer surgery (long-term postoperative morbidity and mortality, hospital stay, readmissions, need of transfer to institution of medium or long stay and quality of life).

Methods

Study design: Patients and participating Centers This is a prospective and multicenter cohort study, within the Spanish EURECCA Esophagogastric Cancer Project, to investigate the impact of frailty on the postoperative results of surgery for gastric cancer in elderly patients. Inclusion/exclusion criteria will be following:

- Inclusion criteria: Patients ≥70 years diagnosed with gastric cancer (whether or not they have received neoadjuvant treatment) and candidates for elective surgical resection with potentially curative intention (R0) even if it is finally an R1 or R2.
- Exclusion criteria: Patients with disseminated gastric cancer or candidates for palliative surgery, as well as those patients who do not give their consent to participate. Participation in the study will be offered to all centers that are currently part of the Spanish EURECCA Esophagogastric Cancer Registry. Those hospitals that show their desire to participate must sign the Letter of Commitment.

The Spanish EURECCA Upper GI Cancer Group was created in 2012 and collects prospective and validated information about all the patients submitted to surgery for esophagogastric cancer in the public hospitals of four Spanish Autonomous Communities, with the aim of having reliable information on the results of this surgery and constitute a platform for the development of research projects.

Data collection

A specific on-line database will be created for this project, with all the security measures (user and password for individual access), in which the researchers will record the data referring to the Frailty and Quality of life questionnaires. On this basis, the researcher will use the patient identifier (random 6-digit code) previously established by the on-line registration of the EURECCA Project where the patients variables are usually collected.

Primary and secondary variables The impact of the frailty on different outcome variables will be evaluated. The main outcome variable will be 90-day mortality after the intervention. Other secondary outcome variables will also be evaluated: incidence of serious complications (Clavien-Dindo complications score ≥ 3), Complication Comprehensive Index (CCI) score (37, 38), hospital stay, incidence of death in patients suffering from a complication (failure to-rescue), hospital readmission within the first 30 days after the discharge, destination of the patient after discharge from hospital [home, social health centers, or geriatric residence], mortality at 12 months after the intervention, quality of life before the intervention and at 12 months.

Frailty evaluation For the assessment of frailty (frailty screening), two questionnaires will be used:

- Questionnaire G8: This is a questionnaire with 8 questions, easy to use, with a total score that varies from 0 to 17 points. Previous studies suggest the score ≤ 14 as a cut-off point to identify the fragile patient, with a sensitivity of 92% and specificity of 52% (36).
- Modified frailty index: This index was described by Velanovich et al. (14), based on a previously validated simplification of the frailty index CSHAFI (Canadian Study of Health and Aging Frailty Index), which was specifically designed to analyze data included in the National Surgical Quality Improvement Program of the American College of Surgeons (ACSNSQIP). It consists of 11 questions with 1 point assigned to each of them on the functional, endocrine, respiratory, cardiovascular and neurological status of the patient. It allows to divide the patients into 4 groups: without frailty (FI = 0), slightly fragile (FI = 1), moderately fragile (FI = 2) and severely fragile (FI ≥ 3).

Postoperative complications Postoperative complications will be classified according to the recommendations proposed by the European Chapter of the International Gastric Cancer Association (EGCA) (unpublished data), its severity through the classification of Clavien-Dindo and the CCI (37, 38). In particular, the CCI will be calculated using the free application that can be found on the website: www.assessurgery.com/calculator_single/.

Health-related quality of life

Health-Related Quality of Life (HRQoL) will be evaluated with the validated Quality of Life questionnaires of the European Organization for Research and Treatment of Cancer (EORTC-QLQ), QLQ-C30 (30 items Core Quality of Life Questionnaire, version 3.0) and with the specific module for gastric cancer QLQ-STO22 (22 items Stomach Quality of Life Questionnaire).

- The EORTC-QLQ-C30 is a questionnaire that reflects the multidimensionality of HRQoL in patients with cancer. It is composed of 30 questions distributed in five functional scales (physical, role, cognitive, emotional and social), three scales of symptoms (fatigue, pain and nausea and vomiting), a global health scale and a series of additional questions to evaluate symptoms commonly referred by patients diagnosed with cancer (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and the perceived financial impact.
- The EORTC-QLQ-STO22 questionnaire contains 22 structured items in five domains (dysphagia, food restrictions, pain, reflux and anxiety) and four specific items (dry mouth, alteration of taste perception, body image and hair loss) related to the symptoms of the disease.

Sample size

The calculation of the sample size is based on the primary objective of comparing fragile versus nonfragile patients with respect to postoperative mortality at 90 days after the intervention. Based on mortality data previously published in a retrospective study by Mosquera et al. (24), it is estimated that mortality for the group of non-frail patients is 0.6% and for the group with frailty 4.3%. From the data of the literature, a prevalence of 23% of frailty is calculated in the population of patients with gastric cancer and age ≥ 70 years undergoing gastrectomy (24). For a power of 80% and a level of significance of 95% in a unilateral analysis, it is estimated that 276 non-fragile patients and 92 fragile patients would be needed to detect as statistically significant the difference between the proportion of patients who die between both groups.

Statistical analysis plan

The characteristics of fragile and non-fragile patient groups will be compared through frequency tables. The Chi-square test will be used to compare the differences between the categorical variables and the ANOVA test for the continuous variables. Different analyzes are proposed according to the study variables that are to be analyzed. For dichotomous type response variables (90- day mortality, 12-month mortality, incidence of serious complications, incidence of in-hospital death in patients with complications, and hospital readmission at 30 days after discharge), a multivariate logistic regression will be used to evaluate the risk (odds ratio) of these variables. For continuous response variables (ICC score) at 30 days after the intervention, and number of days of hospital stay), linear regression models will be used. For the variable categorical response of the patient after hospital discharge, an ordinal logistic regression model will be done. All regression models will be adjusted for age, sex, body mass index (BMI), type of gastrectomy, center volume, neoadjuvant treatment and degree of frailty. Regarding HRQoL analysis, the mean scores and 95% confidence intervals for the different domains of preoperative HRQoL and one year after surgery will be calculated. Changes of more than 10 points on a scale from 0 to 100 will be considered clinically relevant as previously suggested in other publications (40). Work plan The study period includes: Patient recruitment. Follow-up for 1 year to meet the objectives of the study.

The study starts by assessing the fragility of the patients. Once the stage study is completed, the potential curative surgery is determined and after the case presentation in the Multidisciplinary Tumor Committee of each institution, the G8 questionnaires and modified fragility index will be carried out to identify the state and degree of fragility, 2 weeks prior to surgery. The result of the evaluation of the frailty of the patient, will be performed after the Multidisciplinary Committee, thus it will not modify the therapeutic decision.

To measure the Health Related Quality of Life (HRQoL), the QLQ-C30 and QLQ-STO22 questionnaires, will be delivered at the time of the preoperative visit and 12 months after surgery.

Patients will be asked to fill them in their home. If any patient reports difficulty in understanding the questionnaires, additional help will be provided. Once the questionnaires are received, it will be verified that all the questions have been answered. Otherwise, patients will be contacted in order to complete the questionnaire via telephone. If it is not possible to complete the answers of more than half of the questions on a scale, they will be excluded from the statistical analysis, according to the recommendations of the EORTC (39). All responses from the EORTC QLQ-C30 and STO22 questionnaires will be transformed linearly into scores ranging from 0 to 100 to standardize the score. In functional scales, high scores represent better quality of life (better function) while high scores in symptom scales and items involve more symptoms.

In addition, the variables described in the methodology section will be collected and analyzed:

- Incidence of serious complications (Clavien-Dindo complications score ≥ 3)

- Complication Comprehensive Index (CCI) score during the hospital stay and at 30 days after the intervention

- Incidence of in-hospital death in patients suffering from a complication (failure-to-rescue)

- Hospital stay

- Destination of the patient after hospital discharge

- Hospital readmission within the first 30 days after the discharge

- Mortality at 90 days after the intervention

- Mortality at 12 months after the intervention

In addition to the previously described questionnaires and the main and secondary variables, data related to the prevalence of comorbidities of the patients (Charlson Comorbidity Index, ASA), the stage

study, preoperative optimization, surgical intervention, histopathology and follow-up will be collected. All these data are already systematically collected in the EURECCA Register. Ethical considerations This project is included in the EURECCA Registry, which was presented and approved by the Parc de Salut MAR Clinical Research Ethical Committee (CEIC PSMar) in 2013 in its initial version (nº 2013/5047/I). The amendment of the version, dated 9th June 2016, was approved by the CEIC PSMar and by the respective Clinical Research Ethical Committees of the participating centers. The EURECCA Registry also has a specific Patient Information Sheet and Informed Consent, approved in the 1.2 version of March 2018.

The TOREGA study must be approved by the Ethical Committee of each of the participating hospitals (CEIm PSMar nº 2018/7971/I). All patients wishing to participate in the study will sign an Informed Consent in accordance with the ethical standards of the participating institutions.

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