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Fluorescence image-guided lymphadenectomy using indocyanine green and near infrared technology in robotic gastrectomy

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ABSTRACT

Background:

Gastric cancer is a worldwide challenge due to its spread, even epidemic in some areas, and the high mortality rates. Lymphadenectomy is considered the fundamental step during radical gastrectomy. In recent years, some researchers have tried to find a way to improve the surgical identification of the lymphatic drainage routes and lymph node stations. This new surgical frontier is the so called "navigation surgery". Among the different reported solutions, lately, the indocyanine green (ICG) has drawn attention. It is a fluorescence dye, that can be detected in the near infrared spectral band (NIR). The development of specific fluorescence imaging devices has allowed surgeons to visualize tumors, vascular and lymphatic structures. The Da Vinci Xi robotic system has an integrated imaging technology that has been used in colo-rectal and hepato-biliary surgery. However, up to date, the combined use of fluorescence imaging and robotic technology has not been evaluated during lymphadenectomy in gastric cancer.

Methods:

General design: to evaluate the role of fluorescence imaging during robotic lymphadenectomy for gastric cancer.
Type of study: interventional prospective pilot study.
Duration: 18 months.
Experimental group: patients undergoing dissection assisted by ICG.
Control group: patients undergoing the same surgery without the injection of ICG.
Primary outcomes: Fluorescent lymph nodes (FLNs) identification rate, accuracy of the procedure, comparison with the control group on the total number of lymph nodes retrieved.
Sample size: 20 patients in the experimental group, 20 patients in the control group.

Ethics:

This study is conducted in compliance with ethical principles originating from the Helsinki Declaration, within the guidelines of Good Clinical Practice and relevant laws/regulations.

Trial registration number:

NCT03931044

Background:

Gastric cancer is the fourth most widespread cancer in the world and is characterized by high mortality rates [1, 2]. A multidisciplinary context, in which surgery plays the main role, is essential to offer the best therapeutic strategy. Lymph node involvement in gastric cancer is present in 2-18% when the depth of the tumor invasion is limited to the mucosal or submucosal layer, but rises to 50% when the tumor involves the subserosa [3]. Lymphadenectomy is a fundamental surgical phase that must guarantee the oncological radicality and allow an appropriate tumor staging. Although it is among the most relevant factors influencing long-term survival, its extension and standardization is still the subject of much debate. The two latest editions of the JGCA guidelines [4] recommend a dissection on different levels (D1, D1 +, D2) depending on the type of gastrectomy and the clinical stage of the tumor. In recent years, some researchers have tried to apply the concept of "sentinel lymph node" to gastric cancer [5-6]. Although some do not consider that terminology the appropriate one in the context of gastric cancer, because of the multidirectional gastric lymphatic flows, several studies have highlighted interesting aspects, such as: limiting an extensive lymphatic dissection when not necessary, identifying the drainage routes outside the standard anatomical planes, possible assistance in minimally invasive procedures [7]. Most of the experiences in lymph nodes mapping were performed with a radio-isotope (Tc99m) associated or not with the intraoperative use of vital dyes (Blue dye). More recently, the properties of the indocyanine green (ICG) have been studied. This is a fluorescence dye, that can be detected in the near infrared spectral band (NIR) [8, 9]. The development of imaging tools using "Near-Infrared / Indocyanine Green (NIR / ICG)" technology is therefore an innovative approach for visualizing tumors, vascular structures, lymphatic channels, and lymph nodes [10]. Some advantages of the ICG are: reduced toxicity, absence of radioactivity, low cost, safe administration both intravenously and endoscopically through the submucosa or subserosa, protein binding without changing molecular structures, macrophages interaction at the lymph node level. Devices for fluorescence imaging are currently available in both open and minimally invasive surgery. In this field, robotic surgery has been becoming of great interest thanks to the manufacturing of new instruments which, compared to laparoscopy, allow to improve manual skills and gentleness in challenging movements [11]. The Da Vinci Xi robotic system has also produced an innovative imaging technology for ICG visualization made up with a laser source integrated in the robotic camera (Firefly). The surgeon at the console has therefore a 3-D vision that can switch to the fluorescence mode without the need to change the camera. Few clinical experiences have been reported to date [11]. Published articles refer to assistance in colo-rectal and hepato-biliary surgery for vessels or biliary structures visualization, while its use during lymph node dissection for gastric cancer has not yet been the subject of study protocols.

Hypothesis

Fluorescence imaging during lymphadenectomy in gastric cancer can significantly improve the quality of the dissection through a better visualization of anatomical planes and allow tailored dissections. Moreover, the tumor status in the fluorescent nodes could predict the nodes status in the overall specimen with high accuracy rate.

Methods

General study design:

the overall objective is verifying the feasibility and the role of a lymphadenectomy assisted by fluorescence imaging during robotic gastrectomy. Two levels of investigation are planned:

- to detect the possible advantages of a fluorescence-guided surgery ("Navigation Surgery");
- to evaluate the possibility of considering the lymph nodes labeled by the ICG as predictive of the state of tumor diffusion ("Targeted Surgery")

Type of study:

pilot study, interventional prospective study.

Specific aims:

1- To verify the ability of the procedure to highlight the main tumor lymphatic drainage pathways.

2- To validate the concept of Navigation Surgery in gastric surgery by comparing the group of the experimental procedure with a control group undergoing the same type of surgery but not assisted by fluorescence.

3- To find a correlation between the nodes marked by the ICG and the remaining nodes removed during the procedure.

4- To identify the characteristics of those patients in whom the ICG can effectively discriminate the type of lymphadenectomy to be performed.

Eligibility:

- Inclusion criteria: diagnosis of gastric cancer proved through the endoscopic biopsy, cT1 - cT3 and cN0 - N+ at the preoperative staging.
- Exclusion criteria: history of allergies related to iodine, pregnancy, distant metastases, synchronous malignant tumors in other organs, ASA score ≥ 4

Description of the experimental procedure:

the day before surgery, the ICG will be injected endoscopically into the submucosa around the tumor (0.83mg / mL, 0.3mL x 4-6). Each patient will undergo a modified total D2 gastrectomy that includes the following lymph node stations: 1 - 7 + 8a, 9, 11p, 11d, 12a. The lymph node dissection will be performed using the Da Vinci Xi robotic system and the assistance of the near infrared technology to detect ICG fluorescence. Even the resulting fluorescent lymph nodes outside the standard dissection plane will be retrieved. The lymph node stations will be sent to the pathologist in different containers and further subdivided according to fluorescence.

Control group:
data from patients undergoing the same surgery without the ICG imaging procedure will be collected during the same study period.

Data collection:
the following information will be collected for each patient.
- General variables: demographic, histopathological, intra and post-operative features, complications. - Specific variables: total number of lymph nodes retrieved (LNs), Fluorescent lymph nodes (FLNs), metastatic LNs, LNs by station, FLNs outside the standard dissection plane, FLNs status (positive or negative for tumor), non-fluorescent LNs status

Analysis of the experimental procedure:
- FLNs identification rate: patients in which the procedure detects FLNs (%).
- Accuracy: degree of deviation between the FLNs tumor status and the status found in the other LNs analyzed.

Comparison with the control group
- Usefulness of the Navigation Surgery: comparison between the two groups on the total number of LNs retrieved (mean ± SD)
- Impact on the D2 lymph node dissection: comparison between the two groups on the number of LNs removed in the D2 anatomical plane (stations 8a, 9, 11p, 12a) (mean ± SD).

Duration of the project:
18 months.

Institution involved:
Department of Digestive Surgery and Department of Gastroenterology and Endoscopy. St. Mary's Hospital. Terni, Italy.

Sample size:
considering the volume of patients included in published studies available in the literature on the use of fluorescence imaging and adding that the present project is the first to describe the use of robotic technology with fluorescence assistance in gastric cancer, a total of 20 patients will be enrolled for the experimental procedure. An additional sample including 20 patients will be the control group, based on the same eligibility criteria. The total sample of patients planned for the present study is therefore of 40 subjects.

Statistical analysis:
SPSS v23 will be used to perform data analysis. The dichotomous variables will be expressed as numbers and percentages, while the continuous variables as mean and standard deviation, or median and IQR (minimum and maximum values). For the comparison with the control group, the continuous variables will be analyzed with the T test for independent samples and a value of $P < 0.05$ will be considered statistically significant.

Impact on clinical practice and healthcare system
This project can pave the way for a new concept of lymphadenectomy in gastric cancer involving minimally invasive surgery. Patients could benefit from a more tailored approach to their disease.

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Not applicable.

Contributors
JD was involved in conception of the study, JD, AM, ST, AP, VDA were involved in designing the study, analyzing the literature, references searching, drafting the rationale and description of the study methods.

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Competing interests
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval
The study was approved by the ethics Committee of CER Umbria (Prot. No. 15928/19/AV dated 21/03/2019).
This study is conducted in compliance with ethical principles originating from the Helsinki Declaration, within the guidelines of Good Clinical Practice and relevant laws/regulations.

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