

Indocyanine Green-guided Lymphadenectomy in Laparoscopic Total Mesorectal Excision for Low Rectal Cancer After Neoadjuvant Chemoradiotherapy

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Background

Cancer treatment is increasingly oriented toward a personalized medicine. In medical oncology, treatments are often targeted toward specific receptors and cellular pathways, while in surgical oncology a real personalized medicine approach is still a far objective. Indeed, lymph nodes dissection in colorectal cancer surgery is still based on traditional anatomical borders and recently it has been greatly extended routinely in all patients, since a greater harvesting of lymph nodes should mean more accurate pathologic staging and a better disease control.^{1,2}

Despite the correct rationale of this approach, it means to waive the “minimal effective treatment” concept in colorectal surgery, with a tout-court use of wide surgical procedures often burdened by a high intraoperative or postoperative complications rate.³

Currently, in rectal cancer surgery two major issues are still controversial, especially in patients treated by neoadjuvant chemoradiation:

1. The need for harvesting apical lymph nodes at the origin of inferior mesenteric artery for middle-low rectal cancer is still debated.⁴ Indeed, the excision of these lymph nodes could allow a more accurate staging, but the high ligation of inferior mesenteric artery leads necessarily to a greater colorectal resection due to the devascularization of the left colon, with a higher risk of anastomotic leakage and of hypogastric nerves injury. The recent HIGHLOW randomized clinical trial has been conducted on patients affected by rectal cancer, comparing those with a high vs. low ligation of the inferior mesenteric artery. The trial has demonstrated that disease control was similar between groups, but also that long-term genitourinary complications were much more frequent among patients with vessel ligation at the origin.⁵
2. Lateral pelvic lymph nodes dissection is another point of controversy for rectal cancer patients. Indeed, Japanese surgeons perform routinely this dissection, believing that possible residual disease in these lymph nodes is the major responsible for lateral recurrences.⁶ In Europe and in the USA this procedure is not routinely performed, since neoadjuvant chemoradiation is much more administered with a possible impact also on lateral pelvic nodes, also considering the low risk of lateral pelvic nodal metastases.

Based on data retrieved from the cohort of rectal cancer patients treated by neoadjuvant chemoradiation and surgery at the Colorectal Surgery of Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) from 2011 to 2020, the mean number of harvested lymph nodes is 15.8 ± 7.7 . Recently, indocyanine green (ICG)-guided surgery has been introduced in routine clinical practice. ICG is a fluorescent tracer which can be detected by specific cameras for laparoscopic and open surgical procedures. Currently, ICG in colorectal surgery is mainly used to assess the adequate blood supply to the anastomosis.⁷ In other fields, the role of ICG-guided surgery has been explored for lymph nodes dissection such as in breast cancer surgery.⁸

Objectives and endpoints

The primary objective of the study is to assess if the total number of retrieved lymph nodes is superior with ICG-guided surgery compared to standard surgery, in rectal cancer patients undergoing neoadjuvant chemoradiation and subsequent surgery. The primary endpoint of the study is the mean total number of retrieved lymph nodes. Secondary endpoints are the following:

- 1) Number of harvested lymph nodes specifically at the origin of the inferior mesenteric artery
- 2) Number of harvested lateral pelvic lymph nodes
- 3) Intraoperative and postoperative complications rates
- 4) Mean duration of surgery
- 5) Mean duration of the postoperative hospitalization

Type of study

Interventional, non-pharmacological, single-arm study

Inclusion criteria

- Middle-low rectal adenocarcinoma
- Neoadjuvant chemoradiation
- Laparoscopic surgery
- Signed informed consent

Exclusion criteria

- Distant metastases at diagnosis

- Squamous cell carcinoma
- Peritoneal carcinomatosis
- Allergy to ICG

Methods

In all patients, a total volume of 2 mL of ICG (dilution: 5 mg/mL in 10 mL of sterile water) will be injected transanally, administering 0.5 mL of ICG in each peri-tumoral quadrant in the submucosa, 10 minutes before surgery. Surgery will be performed laparoscopically, and a dedicated camera with near-infrared filter will be used to intraoperatively detect ICG-fluorescent lymph nodes. ICG-guided surgery will consist of standard anterior rectal resection with total mesorectal excision, plus the selective excision of extra-mesorectal ICG-fluorescent lymph nodes (origin of the inferior mesenteric artery and/or lateral pelvic nodes). All the other treatments and follow up regimens will be according to the standard of care.

Statistical analysis

The sample size has been calculated based on feasibility criteria, since this is a pilot study. Thus, 30 patients will be accrued in 12 months, also considering a possible drop-out of 10%. The control group will be composed by 30 rectal cancer patients previously treated with neoadjuvant chemoradiation followed by standard surgery, possibly matched by propensity score,

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