COmpletion Sentinel Node resection with or without minimally invAsive and endoscopic cooperative surgery following non-cuRative Endoscopic Submucosal Dissection for Early Gastric Cancer (Co-SNARE-EGC trial)

Background

Early gastric cancer (EGC) is defined as a tumor confined to the mucosa or submucosal layers without lymph node involvement (1). Patients with EGC are typically recommended endoscopic submucosal dissection (ESD) as the first-line treatment, provided they meet the inclusion criteria. The current expanded indications for ESD in EGC include differentiated cancer without ulceration, regardless of size; differentiated cancer with ulceration, provided the lesion is no larger than 3 cm; and undifferentiated cancer without ulceration, with a maximum size of 2 cm(2,3). In some cases, patients may be classified as non-curative (eCuraC2) after ESD due to positive vertical margins, deep submucosal invasion, or lymphovascular invasion. In such instances, complementary surgery is generally recommended (2,3). Gastrectomy with lymphadenectomy carries a risk of severe complications (Clavien-Dindo grade >IIIa) ranging from 8.9% to 22% (4–6), and can significantly affect the patient's health-related quality of life (7). Moreover, many patients may have no residual disease after surgery. A recent multi-center Western study found that 33% of patients who underwent gastrectomy following non-curative ESD had residual tumor, either locally or in regional lymph nodes (8).

Local injection of indocyanine green (ICG) into the peritumoral area has been reported in gastric cancer surgery to identify sentinel lymph nodes, visualize draining lymph nodes, and assess the completeness of lymph node dissection (9). In this phase 1 trial, we aim to evaluate ICG-guided regional lymph node resection, including sentinel node (SN) identification, with complementary laparoscopic and endoscopic cooperative surgery (LECS) as an alternative to gastrectomy following non-curative ESD. For patients with radical but non-curative ESD, ICG-guided SN resection will be performed, while in those with non-radical ESD, LECS combined with ICG-guided SN resection will be performed.

Study design

A single-center, phase-1, prospective non-randomized trial.

Scientific objectives

To study the safety and feasibility of ICG-guided SN with or without additional LECS as an alternative treatment for EGC with previous non-curative ESD

Primary outcome measures

- Safety, defined as Clavien-Dindo complication grade >/= III

Secondary outcome measures

- Any complication (Clavien-Dindo II-IV)
- Postoperative bleeding requiring blood transfusion
- Leakage/postoperative abscess requiring drainage
- Operation time
- pT
- Radicality
- Number of lymph nodes
- Number of positive lymph node
- Hospital-stay
- Health-related quality of life
- 30-day mortality,
- In-hospital mortality
- 1-year disease-free survival

Study population

Patients with EGC previously treated with ESD at our institution will be eligible for inclusion in the study if the resection is non-curative

Inclusion criteria

- EGC previously treated with ESD according to current guidelines (differentiated adenocarcinoma Ulcerative- any size, differentiated adenocarcinoma Ucerative+ </=3cm, undifferentiated adenocarcinoma Ucerative- </=2cm)
- Non curative resection
    - LVI positive
    - R1 vertical margin
    - deep submucosal invasion >Sm1
- Signed informed consent

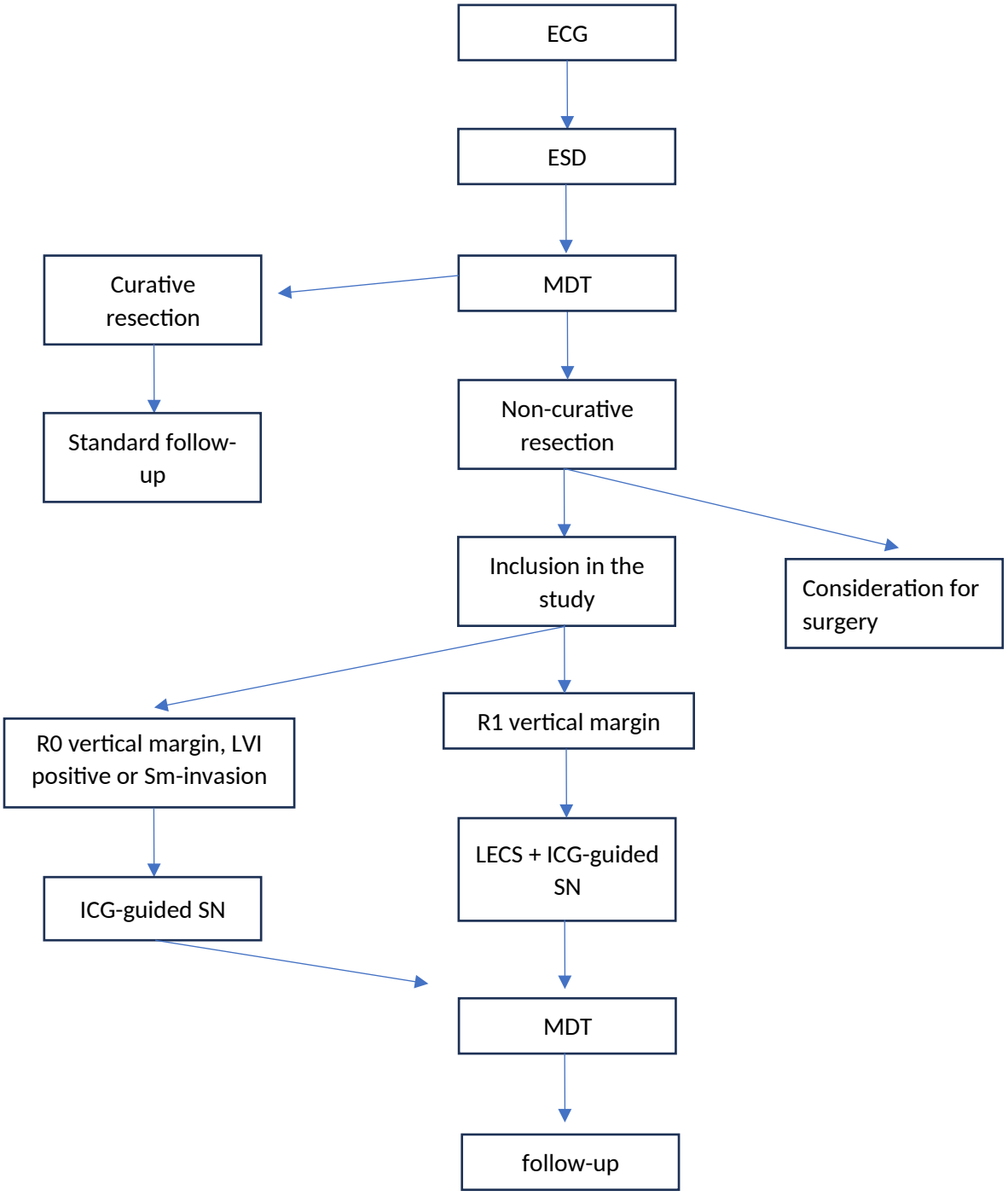
Exclusion criteria

- Location within 2 cm from cardia or pylorus
- Non-curative resection with only R1 horizontal margin
- Inoperative because of severe comorbidities
- Previous radiotherapy to the upper abdomen
- Pregnancy
- Allergy to ICG
- Inability to provide informed consent due to cognitive impairment, language barrier, or other reasons impairing understanding and autonomous decision-making.

The procedure

ICG-guided sentinel node (SN) resection will be performed by endoscopically injecting 0.5 ml of 100-fold diluted ICG at four sites around the tumor scar, followed by resection of the positive lymph nodes after a 15-20 minutes waiting period. LECS will be performed through a combination of endoscopic marking around the scar, dissection using a knife, perforation of the gastric wall, and subsequent laparoscopic resection of the area under endoscopic guidance.

Study flowchart



	Preop visit	ICG guided SN +/- LECS	Postop visit (30 days)	3 months postop – CT + gastroscopy	6 months postop – CT + gastroscopy	9 months postop – CT + gastroscopy	12 months postop – CT + gastroscopy
Information and consent form	x						
Physical & laboratory evaluation	x		x	x	x	x	x
HQL-questionnaires	x		x				x
Review of medical charts			x				x

Assessment of safety

Complications will be continuously monitored for each procedure according to the clinic's routines. An interim analysis will be performed for each 3 cases completed. If any death is observed directly attributed to the procedure the study will be prematurely discontinued. Moreover, the study will also be discontinued if severe complications (Clavien-Dindo complication grade ≥ III) are observed in > 20 % of cases, which is the expected rate for gastrectomy (6).

Follow-up

All patients will undergo an initial postoperative follow-up at the outpatient clinic 30 days after the procedure. Subsequent follow-up visits will occur every 3 months during the first year. During this period, surveillance will include both endoscopic (gastroscopy) and radiological (computed tomography) assessments at 3-month intervals. After the first year, patients will be followed according to the clinic's standard protocol, consisting of physical examination, radiological imaging, and endoscopic evaluation every 6 months for a total follow-up period of 5 years. For patients who die before completing follow-up, the date of death will be documented.

Sample size

We aim to include 10 patients in the study.

Sample size justification

Because this is a pilot study no power calculation is deemed necessary.

Management of data

Information and data from patients included in the study will be handled only by researchers working under confidentiality according to the Health and Healthcare Act. The data will be collected in a database and pseudonymized with study-specific patient codes. All study documentation will be stored in a locked, protected location intended for handling confidential information at Karolinska University Hospital in Stockholm. Only personnel delegated for the study as well as the monitor will have, under confidentiality protection, access to patient records and source data. The code key in these cases will be handled by the appointed research coordinator at the Medical Unit of Upper Abdomen, Karolinska University Hospital in Stockholm. The data material will be destroyed 10 years after publication.

Ethics

The study is conducted in compliance with the protocol and in accordance with the ethical principles of the second Declaration of Helsinki and with GCP rules. The EU General Data Protection Regulation (GDPR) will be respected. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society. Study personnel conducting this trial are qualified by education, training, and experience to perform their respective tasks.

Dissemination of knowledge and publication strategy

The study will be registered at www.clinicaltrials.gov. The protocol will be internationally exposed through a separate publication. Positive as well as negative or inconclusive results will be submitted for publication in international peer-reviewed journals and oral presentations at relevant national and international congresses.

Competing interests

We declare no support and no financial relationships with any organizations that might have an interest in the submitted work.

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