Sentinel node Navigation surgery in early esophageal Adenocarcinoma Patients: the SNAP study

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To evaluate the feasibility and accuracy of sentinel node navigation surgery in patients with early esophageal carcinoma.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON44799

Source
ToetsingOnline

Brief title
SNAP-study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
early esophageal adenocarcinoma, esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: early esophageal adenocarcinoma, sentinel node procedure, treatment

Outcome measures

Primary outcome

- Percentage of patients with a detectable sentinel node, either on SPECT/CT, probe-based and with near-infrared (NIR) camera

- Concordance of pre-operative SPECT/CT and perioperative probe-based and indocyanin green (ICG)-based detection of sentinel nodes

- Number of resected sentinel nodes, location documented

- Number of resected (non-sentinel) lymph nodes, subdivided per lymph node station

- Ratio of number of dissected sentinel nodes and number of detected sentinel nodes on imaging

- Additional yield of ICG-based sentinel node detection over technetium-based sentinel node detection

Secondary outcome

- Procedure time of sentinel node navigation surgery

- Number of tumor-positive lymph nodes, subdivided per lymph node station

- Adverse events

Study description

Background summary

The incidence of esophageal adenocarcinoma (EAC) is increasing in the West (1).
EAC arises from Barrett*s esophagus (BE). In BE, esophageal squamous epithelium

progresses to adenocarcinoma through a multi-step transition consisting of intestinal metaplasia, low grade dysplasia (LGD), high grade dysplasia (HGD), and finally invasive cancer. Patients with known BE are offered endoscopic surveillance. Recent developments, such as the spread of high definition endoscopes through the community, combined with a higher awareness and improved recognition of early lesions in Barrett*s esophagus have led to an increase in detection of early EAC. Early EAC can be treated with endoscopic resection techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) (2). In case of low-risk early EAC (i.e., negative resection margins, histology showing a tumour confined to the mucosa, not poorly differentiated, and absence of vascular or lymphatic invasion), an endoscopic resection is considered to be a curative treatment, since in these lesions spread of tumour cells to the adjacent lymph nodes is highly exceptional (<2%)(3). In case of deep (> 500 micrometers) submucosal invasion, poor differentiation grade, or lymphovascular invasion, the risk of concomitant lymph node metastasis is considered to be too higher, and surgical esophagectomy is recommended in case of acceptable clinical condition (4, 5). However, esophagectomy is a major surgical procedure associated with significant morbidity (up to 40%), mortality (2-4.5%) and reduced quality of life postoperative(2, 6). Our study group investigated a new treatment algorithm for high-risk early EAC, consisting of endoscopic radical (R0) resection of the tumor, in combination with thoracolaparoscopic lymph node dissection without concomitant esophagectomy. Preclinical studies show that thoracolaparoscopic LN dissection is feasible in human cadavers and safe in a porcine survival study (Künzli et al, unpublished data7). This new treatment algorithm might be of great value in the treatment of early esophageal carcinoma, since this may lead to a tailored treatment and might be associated with less morbidity and mortality and a less impaired quality of life compared to esophagectomy because of the less invasive character of the procedure and intact upper-GI functioning. The concept of thoracolaparoscopic lymph node dissection was recently investigated in a human pilot-study (Kunzli et al, unpublished data), in which patients underwent a thoracolaparoscopic lymphadenectomy, directly followed by esophagectomy and gastric tube reconstruction. Results show that a median of 30 lymph nodes was removed, which is comparable with the average number of lymph nodes removed during the standard procedure (esophagectomy with LN dissection). Moreover, the esophagus showed ischemic signs at the end of the lymphadenectomy, implying that such an extensive lymphadenectomy without concomitant esophagectomy might not be as safe as was presumed from the animal data, probably because of too extensive devascularisation of the esophagus. Ideal would be to adjust the lymphadenectomy to the individual patient status, thereby combining a limited dissection of all relevant lymph nodes with preservation of the vascularisation as much as possible. Sentinel node navigation surgery (SNNS) is a concept which is already extensively being used in the treatment of breast cancer and melanoma. A sentinel node is defined as the first lymph node(s) receiving drainage from the primary tumor (8, 9,10). Pathological status of sentinel nodes is assumed to predict the status of locoregional lymph nodes. The extent

of the lymphadenectomy can be tailored according to the pathological status of the sentinel node(s) of the individual patient. In case of a tumor-positive sentinel node, two- or even three-field lymphadenectomy is required, while in case of a tumor-negative sentinel node further lymphadenectomy can be abandoned. During sentinel node navigation surgery, a radioactive tracer is injected peritumoral (or around the resection scar in case of endoscopic resection of the tumor) a day before surgery. Macrophages in the sentinel node absorb the radioactive particles and visualisation and detection is possible through planar images or SPECT/CT images. These images serve as a guide to the surgeon, who identifies the sentinel nodes using a gamma probe and subsequently resects them. Pathological examination reveals if there is evidence of (micro-)metastasis and the extent of lymphadenectomy can be tailored according to the pathological status of the sentinel node(s). Because of a high amount of radioactive tracer at the tumor site (or at the endoscopic resection scar site), peritumoral lymph nodes are hard to visualize with this technique; also known as the shine-through effect. Therefore, peroperative indocyanin green (ICG) is injected peritumoral (or around the resection scar in case of endoscopic resection of the tumor). ICG is a tricarbocyanine dye that has been used clinically for hepatic clearance, cardiovascular function testing and retinal angiography on the basis of its dark green colour. It is a non-specific contrast agent, it does associate with albumin, making it an excellent vascular agent for evaluating both the blood and lymphatic system. ICG binds to plasma proteins and protein-bound ICG emits light with a peak wavelength of 830nm when illuminated by near-infrared (NIR) light (11,12). The excitated ICG can be visualized during surgery with a near-infraredNIR camera and this technique enhances visualization of peritumoral lymph nodes. Combining these two sentinel node techniques has shown promising results in sentinel node mapping in gastric cancer, but has not been evaluated in esophageal cancer (13). Several studies already showed that SNNS is feasible in esophageal cancer and associated with high detection and accuracy rates (88-100% and 78-100%, respectively) and a high sensitivity (78-100%). Early esophageal cancer (T1-tumors) are associated with the best results, while patients with advanced carcinoma are being considered non-suitable candidates because of the destruction of lymph vessels by the tumor and neo-adjuvant therapy and the formation of fibrosis after chemoradiation therapy (10, 11, 12, 13, 14-19). and Takeuchi et al, abstract ISDE 2014). However, none of the available studies investigated the value of SNNS in patients who have undergone an endoscopic resection of an early EAC. Furthermore, studies using an endoscopic gamma probe and subsequently performing a minimally invasive esophagectomy, are scarce. We hypothesize that SNNS might be of great value in early esophageal cancer, especially in the treatment of high-risk early EAC (T1b-tumors). A treatment algorithm consisting of endoscopic resection of the tumor, followed by SNNS and (adjusted) LN dissection may preclude patients with a tumor-negative sentinel node from esophagectomy and associated morbidity and mortality. Before applying this technique in this treatment algorithm however, SNNS needs to be validated in this specific patient group and the surgical team will have to be trained in

performing the procedure.

Study objective

To evaluate the feasibility and accuracy of sentinel node navigation surgery in patients with early esophageal carcinoma.

Study design

In this single-center pilot-study we will include a total of 10 patients with an early esophageal adenocarcinoma (T1).

Intervention

Sentinel node navigation surgery followed by lymph node dissection and esophagectomy (standard care)

Overview sentinel node navigation surgery:

Day before surgery
1. Endoscopic submucosal injection of 0.5cc technetium-99m nanocolloid (total of 100 MBq) 1 day before surgery (maximum of 24 hours) per quadrant in four quadrants in the submucosal layer around the tumor or resection scar in case of performed endoscopic resection.
2. Construction of planar images using a gamma camera, 15-30 minutes and 2 hours after injection of the radioactive tracer.
3. SPECT/CT of chest and abdomen will be performed 2 hours after injection of the tracer. The imaging (SPECT/CT and lymphoscintigraphy) will show the location of the sentinel nodes and thus serves as a guide for the surgeons.

Day of surgery
1. Endoscopic submucosal injection of 0.5ml of indocyanine green (ICG) each injected in four regions in the submucosal layer around the tumor or resection scar.
2. Intra-operative detection of the sentinel nodes (node with the highest radioactivity) using an endoscopic laparoscopic gamma probe (Europrobe 3 system, PI medical) and laparoscopic near-infrared camera. Start with identification in one compartment (thorax or abdomen, depending on the type of anastomosis after esophagectomy)
4. Thoraco- or laparoscopic resection of the sentinel nodes in the first compartment (either thorax or abdomen).
5. Ex-vivo identification of resected sentinel nodes using the gamma probe and near-infrared camera.
6. Rest of lymph node dissection in the first compartment
7. Repositioning of the patient
8. Detection of the sentinel nodes using an endoscopic laparoscopic gamma probe

and near-infrared camera in the second compartment (thorax or abdomen)
9. Thoraco- or laparoscopic resection of the sentinel nodes in the second compartment
10. Ex-vivo identification of resected sentinel nodes using the gamma probe and near-infrared camera.
11. Rest of lymph node dissection in the second compartment and finalisation of esophagectomy with gastric tube reconstruction.
12. Ex-vivo confirmation of absence of sentinel nodes in the esophagectomy specimen using the gamma probe and near-infrared camera.
13. Investigation of the thorax and abdominal cavity with the endoscopic gamma probe to confirm absence of sentinel nodes
14. Finalize esophagectomy and gastric tube reconstruction with cervical or intra-thoracic anastomosis

Study burden and risks

Patients will undergo two extra endoscopies. The first endoscopy is for injection of the radioactive tracer. The second endoscopy (on the day of surgery, when the patient is anesthetized) is for injection of indocyanin green. Upper endoscopy is an investigation which is performed many times a day in the participating hospital. The participating endoscopists are skilled and have vast experience in performing an upper endoscopy.The risks of upper endoscopy are neglectable, and are mainly associated with the introduction of the endoscope and include sore throat and sedation related side effects such as local bruising or pain at the IV site, allergic reaction to the medications and over sedation requiring sedation reversal medications and longer post-procedure observation.
The sentinel node procedure is a procedure which is extensively being used in the treatment of breast cancer and melanomas. Since this is a feasibility study, we do not tailor the lymphadenectomy: all lymph nodes will be removed, regardless of the status of the sentinel node. Oncological result with thus be the same as standard of care. An allergic reaction to the radioactive tracer, dye (indocyanin green) or associated substances might develop, but is rare. Procedure time of surgery will extend to a minimum: we think it will take up to 90 minutes longer compared to surgery without sentinel node navigation surgery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Early esophageal adenocarcinoma, staged as T1 (confined to the mucosa or submucosa)
- Clinical condition allowing esophagectomy
- Signed informed consent

Exclusion criteria

- Esophageal squamous cell carcinoma
- Neo-adjuvant (chemo)radiation therapy
- Other primary tumor
- Known allergy for the radioactive tracer (technetium) or dye (indocyanin green)
- Comorbidity interfering with the procedures
- Unable to provide signed informed consent

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-11-2015
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	27-02-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL51882.018.14