Sentinel node Navigation surgery in early esophageal Adenocarcinoma Patients with lymph node involvement: SNAP-IV study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON50168

Source
ToetsingOnline

Brief title
SNAP-IV study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Early esophageal adenocarcinoma; early esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Early esophageal carcinoma, Esophageal adenocarcinoma, Sentinel node procedure, Treatment

Outcome measures

Primary outcome

The primary outcome for this study is the percentage of patients in whom tumor-positive LN(s) are detected as SN(s), either on SPECT/CT, probe-based or with a NIR camera.

Secondary outcome

The secondary outcomes for this study are:

1) Percentage of patients with a detectable SN, either on SPECT/CT, probe-based or with a NIR camera.

2) Number of resected SN, location documented.

3) Ratio of number of dissected SNs and number of detected SNs on imaging.

4) Number of tumor-positive dissected SNs, subdivided per LN station.

5) Ratio of number of tumor-positive dissected SNs and number of detected SNs on imaging.

6) Concordance of pre-operative SPECT/CT and perioperative probe-based and ICG-based detection of SNs.

7) Additional yield of ICG-based SN detection over technetium SN detection.

8) Number of detectable SNs, either on SPECT/CT, probe-based or with a NIR camera, which could not be dissected during surgery, location and reason documented.

9) Procedure time of SNNS.

10) Incidence and severity of all adverse events.

Study description

Background summary

Esophageal adenocarcinoma (EAC) is the most rapidly rising cancer in the Western World. Barrett*s esophagus (BE) is a premalignant condition predisposing to EAC. Therefore endoscopic surveillance has become standard care for patients with BE in order to evaluate malignant degeneration. Surveillance with biopsy protocols and additional advancements in optics of endoscopes lead to early detection of dysplasia and neoplastic lesions in the esophagus.
Patients with a submucosal EAC are treated surgically in most centers worldwide, since the risk for lymph node (LN) metastases in these tumors is considered to be high. The risk of LN metastasis in submucosal EAC depends on various histopathological characteristics, such as tumor infiltration depth, presence of lymphovascular invasion, and tumor differentiation grade. Based on these histopathological characteristics, submucosal EACs can be divided into two risk groups. In case of a low-risk T1b EAC (i.e., superficial submucosal infiltration <500µm, not poorly differentiated, and absence of lymphovascular invasion), an endoscopic resection (ER) is considered to be a curative treatment, since in these lesions spread of tumor cells to the adjacent LNs is highly exceptional (<2%). The long-term outcome for endoscopically treated patients with low-risk T1b EAC is excellent with reported disease-free survival and overall survival rates of respectively 84% and 84% after 5 year of follow-up. In case of high-risk T1b EAC (i.e., deep submucosal invasion >500µm, and/or poor differentiation, and/or lymphovascular invasion) the risk of concomitant LN metastases is considered to be high, and current guidelines recommend esophagectomy in case of acceptable clinical condition. In patients with high-risk T1b EAC treated with surgery the 5-year disease-free survival and overall survival are respectively 78-89% and 68-70%. However, esophagectomy is a major surgical procedure associated with significant morbidity (up to 45%), mortality (2-4%) and reduced quality of life post-operative.
Our study group therefore stepwise investigated a less invasive, esophageal preserving treatment algorithm for patients with high-risk T1b EAC, consisting of radical (R0) ER of the tumor followed by sentinel node (SN) guided selective lymphadenectomy without concomitant esophagectomy. This new treatment algorithm might be of great value since it is less invasive compared to standard of care, and more importantly, upper-gastrointestinal anatomy remains intact. It might well be associated with lower morbidity and mortality, and therefore might lead to a better quality of life post-operative.
Sentinel node navigation surgery (SNNS) is a concept which is already

extensively used in the treatment of breast cancer and melanoma. During SNNS, a day before surgery a radioactive tracer is injected peritumoral or around the resection scar in case of ER of the tumor. Macrophages in the SN absorb the radioactive particles and visualization and detection is possible through planar images or SPECT/CT images. These images serve as a guide to the surgeon, who identifies the SNs using a gamma probe and subsequently resects them. Pathological status of SNs is assumed to predict the status of locoregional LNs. The extent of the lymphadenectomy can be tailored according to the pathological status of the SN(s). In case of a tumor-positive SN in patients with a submucosal EAC, two- or even three-field lymphadenectomy is required, while in case of a tumor-negative SN lymphadenectomy might be minimized. Several studies showed that SNNS is feasible in EAC and associated with high detection and accuracy rates (88-100% and 78-100%, respectively) and a high sensitivity (78-100%). Early EAC, clinically staged as T1, is 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 neoadjuvant therapy, and the formation of fibrosis after neoadjuvant therapy.

The current study logically follows our previously performed research. Preclinical studies showed that thoracolaparoscopic lymphadenectomy is feasible in human cadavers and safe in a porcine survival study. A clinical pilot-study in patients planned for esophagectomy showed that - while leaving the esophagus in situ - a sufficient number of LNs could be removed (median of 30) during radical lymphadenectomy. However, during this extensive lymphadenectomy discoloration of the esophagus was observed. This could possibly indicate significant damage to the vascularization of the esophagus, an observation not seen in the porcine model. To prevent ischemia of the esophagus, an esophageal sparing radical lymphadenectomy was abandoned and replaced by a more restricted approach using SNNS.

A recent study of our study group investigated the feasibility and accuracy of SNNS using CT-lymphoscintigraphy combined with per-operative gamma probing in 5 patients with a high-risk T1b EAC and planned esophagectomy. In these patients, during endoscopy a radioactive tracer was injected in the submucosa, around the endoscopic resection scar. We could identify and resect SNs in all participating patients (median of 4 SNs) and no AEs occurred. However, upon histological evaluation one LN in the peritumoral region, not identified as SN, contained tumor cells. Because of a high amount of radioactive tracer at the tumor site (or at the ER scar site), peritumoral SNs are hard to visualize; also known as the shine-through effect.

We therefore adapted the protocol incorporating submucosal injection of Indocyanine Green (ICG) combined with a radioactive tracer in four quadrants around the endoscopic resection scar. 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 color. 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 NIR light. The excitated ICG can be visualized during surgery with a NIR camera and this technique enhances visualization of peritumoral LNs. Combining scintigraphy with ICG NIR has shown promising results in SN mapping in gastric cancer.
In our recently finished study (unpublished data, NL61467.100.17) the feasibility of the above mentioned combination of radioactive tracer and ICG was investigated for SN mapping in high-risk EAC. In all five included patients SNs could be detected on lymphoscintigraphy and SPECT/CT (median of 2 SNs). In two patients an additional SN was detected per-operative in the peritumoral region with ICG and NIR, resulting in a median of 3 SNs identified and resected. Thus, combining ICG with scintigraphy enhances the visualization of peritumoral SNs in high-risk EAC.
Currently we are investigating the feasibility and safety of the adapted SNNS procedure in patients with high-risk T1b EAC which have been radically removed by endoscopic resection (NL71361.041.019). As the prevalence of lymph node metastasis in this specific patient category is believed to be low, there is a reasonable chance that none of the included patients in this study will have tumor-positive lymph nodes. Moreover, in all our previous feasibility studies none of the resected SNs were tumor-positive on histopathologic evaluation. However, the therapeutic value of the SNNS procedure is determined by the accurate identification of tumor-positive LNs as SNs. Therefore, we want to perform the SNNS procedure in patients with early EAC and clinical suspicion on LN metastasis in order to obtain evidence that the SNNS procedure can accurately detect tumor-positive LNs as SNs. These patients a

Study objective

The aim of this study is to validate the accuracy of SNNS for the detection of tumor-positive LNs using lymphoscintigraphy with radioactive tracer and NIR with ICG in patients with early EAC with regional LN involvement (clinically staged as T1N1).

Study design

In this multicenter, prospective pilot study we will include up to 5 patients with an early EAC and suspicion of regional LN metastasis, clinically staged as T1N1.

Intervention

Patients will be subjected to a SN procedure. One day before SN procedure patients will undergo an upper endoscopy for submucosal injection of the radioactive tracer (technetium) and indocyanine green in four quadrants around the tumor or the endoscopic resection scar. After injection of the radioactive tracer and dye a lymphoscintigraphy and SPECT/CT will be constructed, which

will show the location of the SNs and thus serves as a guide for the surgeons during the SN procedure. During surgery the SNs will be detected using a laparoscopic gamma probe and a laparoscopic NIR camera, followed by SN guided selective lymphadenectomy. The SN procedure will be followed by lymph node dissection and esophagectomy with gastric tube reconstruction (standard care).

Study burden and risks

Included patients will not have any benefit, apart from the fact that they will contribute to developing a new, less invasive, esophageal preserving treatment for early esophageal cancer and thus possible benefit for patients with esophageal cancer in the future.
The SN procedure is extensively being used in the treatment of breast cancer and melanomas. An allergic reaction to the radioactive tracer, indocyanine green or associated substances might develop. However, in the previous feasibility studies none of the in total 10 included patients developed any signs of an allergic reaction. Patients will be exposed to radiation because they will undergo the lymphoscintigraphy and SPECT/CT. Additional exposure might lead to a slightly increased risk for cancer. However, the amount of extra ionizing radiation in this study is low and therefore the associated risk acceptable. The risks of upper endoscopy are negligible.
The result of the surgical procedure will not differ from daily practice: no additional incisions will be made and oncological result will be the same as standard of care. Procedure time of surgery will be extend to a minimum. We estimate that surgery will take up to 60 minutes longer compared to surgery without SNNS.
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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

Esophageal adenocarcinoma, clinically staged as T1N1M0 with an indication for esophagectomy
Clinical condition allowing endoscopy and surgery
Older than 18 years at time of informed consent
Written informed consent

Exclusion criteria

Esophageal squamous cell carcinoma
Clinically staged as T>1, N>1 and/or M1
Neoadjuvant (chemo)radiation therapy
Known allergy for the radioactive tracer (technetium) or dye (indocyanine green)
Comorbidity precluding endoscopy and/or surgery
Refusing or unable to provide written informed consent

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	99m-technetium-nannocolloid
Generic name:	Nanocoll

Ethics review

Approved WMO Date:	24-03-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-04-2020
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 29572
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-000878-15-NL
CCMO	NL72398.041.19

Study results

Actual enrolment: 0

Summary results
Trial never started