Tailored lymphadenectomy using Sentinel node Navigation surgery in high-risk (sub)mucosal esophageal Adenocarcinoma Patients: SNAP-III study

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The aim of this study is to evaluate the feasibility and safety of new esophageal preserving treatment algorithm for patients with high-risk T1a or T1b EAC consisting of radical ER of the tumor, followed by a SNNS procedure with selective...

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

Summary

ID

NL-OMON49789

Source
ToetsingOnline

Brief title
SNAP-III study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Early esophageal adenocarcinoma; 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,Subsidie KWF Kankerbestrijding

Intervention

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

Outcome measures

Primary outcome

The primary outcomes for this study are:

1) Surgical morbidity, defined as any clinically relevant adverse event which

is related to SNNS

2) Esophageal and gastric functioning, defined as any difference in esophageal

and gastric functioning at 3 months after SNNS compared to baseline, either

observed with HRM or gastric emptying testing

Secondary outcome

The secondary outcomes for this study are:

1) Incidence of local recurrence after treatment with ER and SNNS,

histopathologically proven.

2) Incidence of lymph node metastasis after treatment with ER and SNNS,

confirmed by cytology and/or histology.

3) Incidence of distant metastasis after treatment with ER and SNNS,

histopathologically proven.

4) Percentage of patients with a detectable SN, either on SPECT/CT, probe-based

or with a NIR camera.

5) Concordance of pre-operative SPECT/CT and peri-operative probe-based and

ICG-based detection of SNs.

6) Number of resected SNs, location documented.

7) 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.

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

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

10) Procedure time of SNNS.

11) Incidence and severity of all adverse events.

12) Length of hospital stay (days) after surgical procedure.

13) Quality of life.

14) Surgical mortality, defined as mortality within 30 days after SNNS.

15) Disease-free survival.

16) Overall survival.

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 early EAC may be considered for surgical treatment depending on the risk for LN metastases. The risk of LN metastasis in early EAC depends on various histopathological characteristics, such as tumor infiltration depth, presence of lymphovascular invasion, and tumor differentiation grade. Based on these histopathological characteristics, early EACs can be divided into several risk groups. In case of a low-risk mucosal EAC and low-risk T1b EAC (i.e. superficial submucosal infiltration <500µm, not poorly differentiated, and absence of lymphovascular invasion), an 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 T1 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%. The third risk group involves high-risk T1a EAC (i.e. mucosal invasion with poor differentiation and/or lymphovascular invasion), in which the risk of LN metastasis is recently reported to be higher than previously assumed. Although no clear consensus exists on the best treatment option for this last risk group, some patients with high-risk T1a EAC are referred for surgery. 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 T1 EAC, consisting of radical (R0) ER of the tumor followed by 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-GI 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.
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 an early 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 is expected to be last step before the whole treatment algorithm can be implemented into clinical practice and 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 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). During SNNS procedure a median of 5 SNs were identified and resected of which none were tumor positive on histopathologic evaluation (Overwater et al., unpublished data, NL61467.100.17). Please note that so in all studies so far the SNNS procedure was immediately followed by an esophagectomy with radical lymphadenectomy in the same session.

The current study investigates the feasibility and safety of a new treatment algorithm for patients with high-risk T1a or T1b EAC consisting of radical ER of the tumor, followed by a SN procedure with selective lymphadenectomy by means of scintigraphy with a radioactive tracer (technetium) combined with NIR technology with ICG. In the current protocol, the esophagus is only resected in case of proven tumor positive sentinel node(s).

Study objective

The aim of this study is to evaluate the feasibility and safety of new esophageal preserving treatment algorithm for patients with high-risk T1a or T1b EAC consisting of radical ER of the tumor, followed by a SNNS procedure with selective lymphadenectomy.

Study design

In this multicenter, prospective pilot study we will include a total of 10 patients with a high-risk T1a or T1b EAC.

Intervention

Patients will be subjected to a SN procedure. One day before sentinel node procedure patients will undergo an upper endoscopy for submucosal injection of the radioactive tracer (technetium) and indocyanine green in four quadrants around 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 without concomitant esophagectomy.
After SNNS the follow-up phase starts during the following 24 months. In case of tumor-negative sentinel nodes (most likely the case), patients will enter a strict endoscopic surveillance program by high-definition endoscopy and endoscopic ultrasound. In order to assess the effect of the surgical SNNS procedure on esophageal and gastric motility, assessment of GI tract functioning using high-resolution manometry (HRM) and gastric emptying testing will be done before, and three months after the SNNS procedure. Finally, quality of life will be assessed by means of questionnaires.

Study burden and risks

In patients with a high-risk submucosal EAC, lymph node metastases in earlier surgical series is reported to occur in up to 40% of patients. These series probably overestimate the risk, and have understaged the esophageal tumor. In recent series, in which patients with a high-risk submucosal EAC were treated surgically or endoscopically, we found an incidence of 16%. Moreover, the number of tumor-related deaths in both groups (surgical vs. endoscopic treatment) was equal (12%) and invasive surgical treatment did not cure all patients: still some patients developed metastatic disease.
Recently, we analyzed a cohort (n=18) of patients with a high-risk submucosal EAC which were treated endoscopically, and underwent endoscopic follow-up. After a median of 23 months of follow-up, none of these patients has developed lymph node metastasis. We therefore hypothesize that the risk for lymph node

metastasis in these tumors is much lower than reported in earlier surgical series, and that selective lymphadenectomy using SNNS is justified.
In patients with high-risk mucosal EAC, a recent retrospective analysis from our research group has showed that the risk of LN metastasis is comparable to the risk in patients with high-risk submucosal EAC. During a median follow-up of 31 months, 6 of 27 patients (22%) with high-risk T1a EAC were diagnosed with LN metastasis. Although the risk of LN metastasis in this specific patient category is higher than previously assumed, the majority of patients with high-risk mucosal EAC will not develop LN metastasis. Therefore we believe that these patients may also benefit from a selective lymphadenectomy using SNNS. We are unsure however, about the risk of developing lymph node metastasis after resection of tumor-negative sentinel nodes. We think this risk is very low (in line with literature on SNNS in breast cancer and melanoma). In either way, we will keep patients under strict endoscopic follow-up with EUS to be able to detect lymph node metastasis as soon as they develop. When lymph node metastasis will occur, patients will be discussed in a multidisciplinary meeting and most optimal treatment will be determined.
The SN procedure is extensively being used in the treatment of breast cancer and melanomas. Possible risks include an allergic reaction to the radioactive tracer or associated substances, which is extremely rare, and exposure to radioactive beams, of which the amount stays below the maximum threshold. The risks of upper endoscopy, upper gastrointestinal functioning tests and PET-CT are negligible. They 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 I.V. site, allergic reaction to the medications or I.V. CT contrast medium and over sedation requiring sedation reversal medications and longer post-procedure observation. Medications used for conscious sedation are carefully titrated and monitored based on the patients' arousal levels and vital signs.

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

High-risk mucosal or submucosal EAC, clinically staged as T1N0M0
Tumor-free deep vertical resection margins in the endoscopic resection specimen
Clinical condition allowing endoscopy and surgery
Signed informed consent

Exclusion criteria

Esophageal squamous cell carcinoma
Neo-adjuvant (chemo)radiation therapy
Other primary tumor with a life expectancy <3 years
Known allergy for the radioactive tracer (technetium) or dye (indocyanin green)
Comorbidity precluding endoscopy and/or surgery
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:	Completed
Start date (anticipated):	30-01-2020
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	02-01-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2021
Application type:	Amendment
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: 25137
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL71361.041.19