Endoscopic management of patients with high risk T1a and T1b N0M0 esophageal adenocarcinoma: a prospective multicenter registry

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To evaluate the safety of an endoscopic follow-up strategy in patients with HR T1a and T1b N0M0 esophageal adenocarcinoma (EAC).

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

Summary

ID

NL-OMON54809

Source
ToetsingOnline

Brief title
PREFER study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
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: Endoscopic follow-up, Endoscopic treatment, High risk mucosal EAC, High risk T1a EAC, Submucosal EAC, T1b EAC

Outcome measures

Primary outcome

1.5-year disease-specific mortality/survival

2.Overall survival

Secondary outcome

1. Lymph node metastasis, confirmed by cytology and and/or histology .

2. Local recurrence eligible for endoscopic therapy

3. Local recurrence requiring surgical therapy

4. Distant metastasis, histopathologically and/or cytologically proven.

5. Quality of life

Study description

Background summary

Over the last decades, the treatment of early adenocarcinoma has shiftes from surgical treatment to endoscopic treatment. Endoscopic treatment has been established as first choice treatment for low risk mucosal EAC, with excellent efficacy and safety, also in long-term analyses. Endoscopic resection (ER) offers local treatment and does not include lymph node dissection as is still standard of care during esophagectomy. Therefore, the choice to perform endoscopic follow-up after a radical ER of an early EAC, or to refer a patient for additional surgery, is guided by the assumed risk of lymph node metastasis. This risk is assessed by taking into consideration histopathological risk factors such as tumor infiltration depth, differentiation grade, presence of lymphovascular invasion, and the radicality of the endoscopic resection at the deep vertical resection margin. Indications for endoscopic management are EAC*s limited to the mucosa (T1m1-3), with good to moderate differentiation (G1, G2), without lymphovascular invasion, which were radically resected (R0). Relative indications for endoscopic resection are high risk mucosal EAC*s with

lymphovascular invasion and/or poor differentiation, and low-risk submucosal EAC*s. No data exists on the risk of lymph node metastasis in high risk T1a EAC, however, recent retrospective analysis shows that this risk may be higher than previously assumed. Low risk submucosal EACs are defined as cancer limited to the upper 500 microns of the submucosa, good to moderately differentiated (G1-G2), and no lymphovascular invasion, which are radically resected. Based on s studies the risk of lymph node metastasis in these submucosal cancers is <2%., which is lower than the mortality risk of esophagectomy. Patients with a high-risk submucosal EAC (deep submucosal infiltration >500nm, and/or poor differentiation (G3), and/or presence of lymphovascular invasion are considered surgical candidates. Traditionally, the risk of lymph node metastasis associated with submucosal EAC was considered too high to offer these patients endoscopic follow-up. Only in elderly patients with comorbidity, more often an endoscopic protocol is selected. However, the risk of lymph node metastasis associated with submucosal EAC*s is mainly based on surgical series. Recently a number of studies, which included patients treated endoscopically, were published indicating that the risk of lymph node metastasis may however be lower than generally assumed.Therefore, a less invasive and organ preserving approach may not only be an option in the frail and elderly, but for all patients with submucosal EAC*s.

Study objective

To evaluate the safety of an endoscopic follow-up strategy in patients with HR T1a and T1b N0M0 esophageal adenocarcinoma (EAC).

Study design

Prospective international multicenter cohort study.

Intervention

After endoscopisc treatment: endoscopic follow-up with frequent endoscopies and EUS.
Intervals:

year 1 en 2: 3-4-monthly gastroscopy + EUS.
1 year after baseline endoscopy single CT-thorax/abdomen.
year 3 en 4: 6-monthly gastroscopy + EUS
year 5: 1x per year gastroscopy + EUS

Study burden and risks

Potential benefits: Included patients will not undergo esophagectomy with lymphadenectomy as an additional treatment directly after ER. Esophagectomy is associated with significant morbidity of up to 50%, mortality of 2-4% (even in

expert centers) and a temporary reduced quality of life. Moreover, the digestive system is significantly affected, leading to a whole different life (eat) style. Included patients will be followed endoscopically, which is far less invasive than undergoing major surgery. We therefore hypothesize that their quality of life will be less affected compared to patients undergoing esophagectomy. Potential risks: The field for endoscopic therapy in submucosal EAC is expanding. Currently, endoscopic therapy for so called *low-risk* submucosal EAC is justified. These are superficial submucosal tumors (<500nm), which are good to moderately differentiated (G1-2), without presence of lymphovascular invasion, which are radically resected. The risk of lymph node metastasis in these tumors is close to zero (<2%), and does not exceed the mortality risk of esophagectomy. Therefore, endoscopic therapy is considered to be curative. For patients with high-risk mucosal EAC no evidence on the risk of LNM exists, except for our recent retrospective analysis performed in 9 Dutch Barrett Expert Center which showed higher risk of LNM in the high risk T1a group than in both T1b (LR and HR) groups. For patients with high risk T1a EAC, endoscopic treatment and FU already is a relative indication. Including them in our prospective analysis will not bring any potential risks. For patients with a high-risk submucosal EAC, standard of care is to undergo esophagectomy with lymphadenectomy. In this study, patients will not undergo surgical treatment, but undergo upper endoscopies and EUS at regular time intervals. It might be the case that the cancer will return. Majority of these local recurrences can be treated endoscopically. In some cases the lesion cannot be treated endoscopically. In that case, patients will be discussed in a multidisciplinary meeting to determine which treatment is indicated regarding patient*s age, comorbidities and preferences. In patients with a high-risk submucosal EAC, the associated risk of lymph node metastasis is estimated to be about 16%. Far majority of patients with a submucosal EAC therefore undergoes major surgical treatment without finding any cancer cells in the esophagus or lymph nodes. Moreover, esophagectomy is a procedure associated with significant morbidity (up to 50%) and mortality (2-4%). If patients do develop lymph node metastasis during follow-up, patients will be discussed in a multidisciplinary meeting to determine optimal treatment. Standard of care in case of N+ disease is to administer neoadjuvant chemoradiation therapy followed by surgery. Depending on age, comorbidities and patient*s preference, the treating physician will determine which treatment is indicated. Upper endoscopy is an investigation, which is performed many times a day in all participating hospitals. The participating endoscopists are skilled and have vast experience in performing an upper endoscopy. The risks of upper endoscopy and endoscopic ultrasound are negligible, 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. All patients undergoing endoscopy are monitored with continuous pulse oximetry and vital signs assessment (blood pressure) during the procedure. 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

1. Patients with high risk mucosal or submucosal EAC diagnosed in an ER specimen, diagnosed by an expert gastrointestinal (GI) pathologist.
2. Signed informed consent.

Exclusion criteria

1. Prior history of esophageal cancer (invasion of T1sm or deeper or HR T1a).

2. Synchronous esophageal squamous cell carcinoma
3. Suspicion on lymph node metastasis or distant metastasis on EUS, ultrasound of the neck, CT-thorax-abdomen or PET-CT during baseline measurement.
4. Tumor-positive deep resection margin (R1) in ER/ESD specimen
5. Patients unable to give signed informed consent.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-08-2017
Enrollment:	175
Type:	Actual

Ethics review

Approved WMO Date:	12-06-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-11-2018
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	11-05-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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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
ClinicalTrials.gov	NCT03222635
CCMO	NL61165.018.17