FEASIBILITY OF SENTINEL NODE DETECTION IN ESOPHAGEAL CANCER

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To test the validity and feasibility of this concept in GI cancers, we propose a radio-guided intraoperative sentinel node procedure using preoperative endoscopic submucosal injection of radioactive tracer followed by intra-operative gamma-probing.

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal ulceration and perforation
Study type	Interventional

Summary

ID

NL-OMON30292

Source
ToetsingOnline

Brief title
FEASIBILITY OF SN IN ESOPHAGEAL CANCER

Condition

- Gastrointestinal ulceration and perforation

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: ESOPHAGEAL CANCER, SENTINEL NODE DETECTION

Outcome measures

Primary outcome

All resection specimens will be assessted by a senior pathologist. Specimen analysis will be performed in a standardized fashion with prospective documentation of all assessed parameters. Classification of the depth of tumor infiltration will be performed according to standard criteria into high-grade intraepithelial neoplasia, carcinoma limited to the mucosa (pT1a category), and carcinoma invading the submucosal layer but not beyond (pT1b category). The tumor with the deepest depth of infiltration or largest diameter will be chosen as the main tumor.

All removed lymph nodes will be identified according to their location (celiac axis, left gastric artery, lesser gastric curvature, left and right paracardial, paraesophageal distal in the posterior lower mediastinum, bifurcation, and upper mediastinum), counted, and assessed separately. Standard histopathologic analysis of lymph nodes will be performed by serial sections of 5-µm thickness and staining with hematoxylin-eosin and van Gieson. Immunohistochemistry will be performed to search for lymph node micrometastases in all patients staged as pN0 on standard histology as described previously.

Lymphatic vessel invasion (also termed lymphangiosis) is defined as tumor cell

spread through the lymphatic vessels (ie, carcinoma cells floating within the endothelial-lined space).

Routine follow up will be performed by the oncologic outpatient clinic or the patient's general practitioner.

The follow up of these patients will be 24 months.

All evaluated parameters will be prospectively documented throughout the study period in a dedicated database.

Tested variables included *histologic tumor type* (adenocarcinoma vs squamous cell carcinoma), *depth of tumor infiltration* (HGIEN/pT1a vs pT1b), *number of removed nodes,* *presence of lymph node metastases* (pN0 vs pN+), *surgical approach* (abdominothoracic vs radical transhiatal), and *tumor location* (above/at vs below the level of the tracheal bifurcation).

All analyses will be performed using the statistical package SPSS for Windows.

Secondary outcome

nvt

Study description

Background summary

In the twentieth century, lymph node dissection based on metastatic distribution has developed as the standard procedure for surgical management of gastrointestinal cancer.

The fear that invisible micrometastases might be present has encouraged aggressive resection with lymphadenectomy to control the disease.

However, the prognostic benefits of extensive surgery are still unknown and the universal application of radical surgery may affect surgical morbidity, mortality, and quality of life after surgery, particularly in patients without lymphatic spread.

In the twenty-first century, a novel technology to detect micrometastases without extensive surgical resection is required to establish an individualized surgical management approach to gastrointestinal cancer.

Lymphatic mapping techniques are now used in the control of superficial malignancies, such as malignant melanoma and breast cancer, providing a novel tool that may also be of use for gastrointestinal cancers [1]

Although the sentinel node concept has been validated and clinically applied to breast cancer and malignant melanoma, its clinical significance in other solid tumors has not been thoroughly investigated.

Esophageal cancer is a particularly aggressive GI malignancy because of the high incidence and widespread distribution of lymph node metastasis. However, the SN concept seems to be applicable according to recent reports.[8,9]

There are several specific features of SN mapping in esophageal cancer:

o A dye-guided method is not applicable for esophageal cancer because of its anatomical situation. It is impossible to trace the flow of blue dye without destruction of the lymphatic network.

o SNs in esophageal cancer are multiple and distributed widely from the cervical to the abdominal area. Therefore, the lymphoscintigram is essential to identify the SNs in esophageal cancer.

o Recently, chemoradiotherapy (CRT) has attracted attention as a multidisciplinary curative treatment for cT1N0 esophageal cancer. In this approach, control of micrometastasis is essential. Lymphoscintigrams revealing the distribution of SNs in each individual case are useful to design the field of irradiation.

o A complete sampling of multiple and widespread SNs in esophageal cancer is not a minimally invasive procedure, unlike in breast cancer. At present local resection of a primary esophageal cancer with negative SNs is not practical. However, selective and modified lymphadenectomy for clinically N0-stage esophageal cancer should become feasible and clinically useful.

o Although three-field lymph node dissection is recognized as an extensive and curative procedure for thoracic esophageal cancer, its prognostic significance is still controversial. Uniform application of this highly invasive procedure may increase the morbidity and reduce quality of life after surgery.

o Individualized selective lymphadenectomy for clinically N0-stage esophageal cancer based on SN status would be a reasonable surgical approach.[10]

o If mediastinal SNs are all negative and no hot spot is detected in the cervical area by preoperative scintigraphy, cervical lymph node dissection would not be necessary.

o Approaches for lower thoracic and abdominal esophageal cancer, including Barrett*s adenocarcinoma, could be individualized by SN status. If abdominal SNs are all negative and no hot spot is detected in the mediastinal area by preoperative scintigraphy, transthoracic extensive lymph node dissection is not required. [2]

With regard to gastrointestinal (GI) cancers in particular, surgeons have been cautious because of the high frequency of skip metastasis and the complicated lymphatic system in the GI tract. The so-called skip metastasis has been defined according to anatomic classification of regional lymph nodes and that the lymphatic drainage route must be patient or lesion specific.

In a recent study 131 patients with GI cancers (esophagus: 22, stomach: 71, colorectum: 38), the detection rate of sentinel nodes was 91% and overall diagnostic accuracy of lymph node metastasis by sentinel node status was 97%. Initial results suggest further investigation of this procedure as an accurate staging and a minimally invasive approach to early GI cancers.[4]

In the Tsioulias's study lymphatic mapping (LM) was performed in 65 patients with GI neoplasms by injecting 0,5 to 1 ml of isosulfan blue dye around the

periphery of the neoplasms [7]. Blue stained SNs were analysed by hematoxilin-eosin staining, multiple sectioning, and cytokeratin immunohistochemistry.

The author underlines that the LM can identify aberrant lymphatic drainage, which may alter the extent of resection. Aberrant drainage patterns are not uncommon in patients with GI neoplasms, and they are a possible explanation for inadequate staging and a patient's failure to respond to adjuvant treatment [7].

Tsioulias concludes that in the meantime LM with focused examination of the SNs (on serial sectioning and IHC) improves the staging of GI neoplasms and may affect the selection of the patients for adjuvant therapy. Eventually, according to the Maruyama opinion, the ability to identify a tumor free SN might enable the surgeon to avoid the morbidity associated with radical lymphadenectomy in patients with GI cancer [9].

Until the late 1990s, the application of the sentinel node (SN) concept to gastrointestinal (GI) malignancies was not recognized because of the multidirectional and complicated lymphatic flow from the GI tract. However, several studies supporting the validity of the SN concept for GI cancers have been reported in the past 5 years.

Because of its anatomical location, gastric cancer is one of the most suitable targets for minimally invasive surgery based on SN status. Laparoscopic local resection is theoretically feasible for curative treatment of SN-negative early gastric cancer.

Although SNs in esophageal cancer are multiple and are distributed widely from the cervical to the abdominal area, selective and modified lymphadenectomy for clinically N0-stage esophageal cancer is likely to become feasible and clinically viable. Total mesorectal excision (TME) is accepted as a standard surgical procedure for rectal cancer. However, there is a risk of aberrant distribution of SNs beyond the extent of TME; for example, SNs may be lateral to the lower rectum. SN mapping with scintigraphy is useful for effective sampling of SNs in unexpected areas and accurate staging without extensive lymph node dissection.

There are several practical issues to be overcome. The techniques and feasibility of laparoscopic SN sampling are still under investigation. Large-scale multicenter prospective validation studies for SN mapping in GI cancer are essential. If these remaining issues can be solved, SN mapping for GI cancer will have great clinical impact [2].

Study objective

To test the validity and feasibility of this concept in GI cancers, we propose a radio-guided intraoperative sentinel node procedure using preoperative endoscopic submucosal injection of radioactive tracer followed by intra-operative gamma-probing.

Study design

prospective study

Intervention

LYMPHOSCINTIGRAPHY

Tracer injection

The patient is seen in the Department of Gastoenterology on the afternoon before the day of the surgery, or in the morning of the day of surgery.
Before surgery, 0.5 ml 40 MBq of Tc-99m colloid albumine (Nanocoll) will be injected endoscopically into four submucosal sites surrounding the tumor.
Injections will be performed with 23-gauge endoscopic injection sclerotherapy needles.
The total dose injected into each patient will be 160 MBq (4,5 mCi) [13].
The time interval between injection of the tracer and surgery should be al least two hours to allow the tracer to reach the drainings lymph nodes.

Imaging and reporting

Dynamic images starting shortly after injection during 30 minutes are helpful to depict the SN.

Static lymphoscintigraphy (128x128 matrix) is performed 2 hours after injection of the tracer and may be repetead 1-2 hours before operation.

The following thorax and abdomen views are advised: anterior, left and right lateral.

The use of a flood source to delinate the body contour are helpful.

The images should be discussed with the surgeon pre-operatively and should be available during surgery.

6. SURGICAL APPROACH

Surgery should be performed within 24 hours after injection of the tracer.

The standard surgical approach will be an abdomino-right-transthoracic en bloc esophagectomy with 2-field lymphadenectomy for squamous cell cancer and a radical transhiatal tumor resection with extensive lymphadenectomy in the lower posterior mediastinum in patients with adenocarcinoma of the distal esophagus.

The extent of lymphadenectomy in the upper abdominal compartment and lower posterior mediastinum will be identical for all surgical approaches and comprised a suprapancreatic lymphadenectomy, including all lymph nodes along the common hepatic artery, celiac axis, and splenic artery toward the splenic hilum. Also will be included all lymph nodes along the proximal two thirds of the lesser gastric curvature and the gastric fundus, left and right paracardiac nodes, distal paraesophageal nodes, and nodes in the lower posterior mediastinum up to the tracheal bifurcation.

With the transhiatal approach, this will be achieved after a wide anterior splitting of the diaphragmatic hiatus and transhiatal exposure of the lower posterior mediastinum.

Patients with an abdomino-right-thoracic approach will have an additional formal extended mediastinal lymphadenectomy comprising all nodes at the tracheal bifurcation along the left and right main stem bronchi, the upper mediastinal compartment, and along the left recurrent nerve.

Study burden and risks

Based on a standard tracer dose of 160 MBq the maximum total body amount of radiation absorbed by the surgeon will be 15 microSv/hr. The maximum amount of radiation allowd per year for the hands, that are the most exposed during the procedure, is 15 milliSv. Most of the radiation dose is coming from the injection site, only a few percent originates from the sentinel node.

Exposure of the other operating staff and pathology staff will be lower as the distance to the radiation source is further and the exposure time is shorter.

For transportation within the hospital a leakproof bag or box will be suffice.

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

* patient has to be fit to undergo SN biopsy/surgery;* before registration for this study, informed consent must be obtained ;* absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.;* no metastatic disease;* no previous treatment of cancer

Exclusion criteria

-metastatic disease
-previous treatment of cancer

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2006
Enrollment:	25
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL15446.058.06