Real time Molecular Fluorescence and Narrow Band Imaging for detection of the Primary Cancer Lesion in Patients with a Metastatis of Unknown Primary Tumor in the Head and Neck

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This study has been transitioned to CTIS with ID 2024-513897-23-00 check the CTIS register for the current data. The main objective of this study is to evaluate the use of molecular fluorescence imaging using cetuximab-IRDye800CW in the detection of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON54715

Source
ToetsingOnline

Brief title
REFLECT

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
cancer of unknown primary, head & neck cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: EGFR, Fluorescence, Unknown primary tumor

Outcome measures

Primary outcome

- Macroscopic fluorescent signal levels (TBR) and tracer distribution observed

by molecular fluorescence imaging using the multispectral F2 camera system;

- Number and extension of detected lesions with (pre)malignant vascular

patterns.

- Standard histopathological assessment (i.e. hematoxylin and eosin staining)

to correlate fluorescent and non-fluorescent areas detected in vivo with

histology using in vivo obtained biopsies;

- EGFR expression by means of EGFR immunohistochemistry.

Secondary outcome

See above

Study description

Background summary

Cancer of unknown primary (CUP) is defined as the presence of histologically proven metastatic disease for which the site of origin cannot be identified at the time of diagnosis. In this study, we focus squamous cell carcinoma metastases in the upper neck i.e. level 1-3 from an unknown primary tumor most likely located in the upper aerodigestive tract. In current diagnostic work-up comprising PET/CT, panendoscopy and (random) biopsies, 53.4% of these CUPs remains undetected. In this case, the treatment may consist primarily of

(chemo)radiation or (modified) radical neck dissection followed by adjuvant radiotherapy of the neck and the possible locations of the unidentified primary tumor. Recently it was shown that in case of CUP without identification of the primary tumor, survival increases when a ipsilateral tonsillectomy is performed. However, accurate identification of the primary tumor is very important in order to apply optimal treatment. If the primary tumor is detected, the treatment can be focused on the primary site which improves therapeutic efficiency and decreases treatment-induced morbidity.
Clearly, new endoscopic *real-time* imaging techniques are needed to visualize mucosal changes associated with head and neck squamous cell carcinoma and increase detection rate of the primary tumor. Molecular fluorescence imaging enables the visualization of targeted tumor-specific biomarkers by using fluorescence, thereby enhancing the contrast between normal mucosa and tumor tissue. This could improve the detection of the primary tumor. Narrow band imaging enhances visualization of changes in vascularization associated with (pre)malignant lesions. It has been investigated previously with studies reporting that it is superior to white-light imaging by enabling accentuation of abnormalities in vasculature of mucosal lesions, however its application in patients with CUP needs to be further investigated.

Study objective

This study has been transitioned to CTIS with ID 2024-513897-23-00 check the CTIS register for the current data.

The main objective of this study is to evaluate the use of molecular fluorescence imaging using cetuximab-IRDye800CW in the detection of the primary tumor in patients with CUP. In addition, we aim to assess the accuracy of these imaging modalities in terms of detection rate, sensitivity, specificity, positive and negative predictive value.

Study design

The current study is a non-randomized, non-blinded, prospective, single center, phase I diagnostic study. 35 patients with CUP will be included. Patients will be administered with 15 mg or 50 mg cetuximab-IRDye800CW.

Intervention

Patients will - after written informed consent - receive an intravenous injection of the fluorescent tracer. Two days later, panendoscopy will be performed.

Study burden and risks

Burden

- Time investment: Patients need to visit the UMCG two to four days before their planned surgery which will take approximately 2 hours. Also, a day before the planned procedures, patients will receive a laryngoscopy. Usually patients are admitted on the day of panendoscopy. Therefore the measurements on this day will not require extra time investment
- Extra procedures: 1) Intravenous administration of cetuximab-IRDye800CW. 2) The estimated time for taking fluorescence images is approximately 30min. Therefore the time under general anesthesia will be prolonged. 3) Biopsies will be taken from suspect areas based on fluorescent or NBI signal.

Risks
Allergic reactions to cetuximab have been reported but this is considered a low risk. No preclinical or clinical study reported higher than grade 2 adverse events. In the first study with cetuximab-IRDye800CW, no serious events were reported in six patients. In an ongoing study at the UMCG at the Department of Oral and Maxillofacial Surgery, no serious events have been reported.

Benefit
Patients may have benefit from this study directly. The panendoscopy procedure will be planned as usual. During panendoscopy, biopsies will be taken based on fluorescence and narrow band imaging. The benefit of this study will be that identification of the primary tumor by means of this biopsies may lead to a treatment plan focused on the primary tumor lesion instead of a morbid treatment of the whole upperaerodigestive tract. Furthermore, the results of these types of study will be at least beneficial for other patients with cancer in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Cytology confirmed diagnosis of squamous cell carcinoma and scheduled to undergo panendoscopy as decided by the Multi-Disciplinary Head and Neck Tumor Board of the UMCG;
- The primary tumor was not identified during standard diagnostic work-up in the outpatient clinic including physical head and neck examination, laryngoscopy, X-thorax and CT, PET or MRI;
- Age >= 18 years;
- Written informed consent;
- Mentally competent person that is able and willing to comply with study procedures.

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent;
- Concurrent uncontrolled medical conditions;
- Received an investigational drug within 30 days prior to the dose of cetuximab-IRDye800CW;
- History of myocardial infarction, cerebrovascular accident, uncontrolled cardiac heart failure, significant liver disease or unstable angina within 6 months prior to enrollment;
- Inadequately controlled hypertension with or without current antihypertensive medications;
- History of infusion reactions to cetuximab or other monoclonal antibody therapies;
- Pregnant or lactating women. Documentation of a negative pregnancy test must be available for women of childbearing potential. Woman of childbearing potential are premenopausal women with intact reproductive organs and women

less than two years after menopause;
- Evidence of QT prolongation on pretreatment ECG (greater than 440 ms in males or greater than 450 ms in females);
- Patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents;
- Clinically significant abnormalities in magnesium, potassium and calcium levels;
- Life expectancy < 12 weeks;
- Karnofsky performance status < 70%.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-04-2023
Enrollment:	35
Type:	Actual

Medical products/devices used

Generic name:	intraoperative fluorescence camera system
Registration:	No

Ethics review

Approved WMO

Date:	13-07-2018
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EU-CTR	CTIS2024-513897-23-00
EudraCT	EUCTR2018-001885-41-NL
ClinicalTrials.gov	NCTnummervolgt.
CCMO	NL65892.042.18