Image guided surgery for margin assessment of cutaneous squamous cell carcinoma during surgery: a phase I proof of concept study

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The main purpose of this pilot study is to investigate the feasibility of fluorescence imaging using cetuximab-IRDye800CW for intraoperative margin assessment in patients with cutaneous squamous cell carcinoma.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49316

Source
ToetsingOnline

Brief title
Image guided skin cancer surgery

Condition

- Skin neoplasms malignant and unspecified

Synonym
skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: KWF

Intervention

Keyword: Cutaneous squamous cell carcinoma, EGFR, Near-infrared fluorescence, Optoacoustic imaging

Outcome measures

Primary outcome

- Macroscopic fluorescent signal levels (TBR) and tracer distribution observed by NIR fluorescence imaging using the intraoperative in vivo imaging as well as the ex vivo back-table imaging;

- Quantification of fluorescent signals using MDSFR/SFF spectroscopy;

- Standard histopathological assessment (i.e. haematoxylin and eosin staining) to correlate fluorescent and non-fluorescent areas detected in vivo with histology using surgical specimen;

Secondary outcome

- Patient characteristics (age, sex, BMI, history and morbidity, localization and classification of cancer, treatment outcome, blood pressure, pulse and temperature before and after tracer administration, signs and symptoms before and after tracer administration).

- Histopathologic examinations related to ex vivo EGFR expression and cetuximab-IRDyeCW800 distribution.

- Quantification of the cetuximab-800CW optoacoustic signal and the tracer distribution observed by multispectral optoacoustic imaging using the MSOT Acuity Echo in vivo.

Study description

Background summary

The gold standard of treatment in non-melanoma skin cancer (NMSC) is wide surgical excision. During surgery, it is hard to discriminate between tumor and normal tissue using visual and tactile information. Even with the use of perioperative fresh frozen sections, there is a significant risk of a tumor-positive margin post-operatively. Micrographic surgery techniques have been developed to ensure the complete removal of tumor tissue, while maximizing normal tissue conservation. Mohs Micrographic Surgery (MMS) is recommended for high-risk and recurrent basal cell carcinoma, cutaneous squamous cell carcinoma (cSCC) and other uncommon skin tumors (1). In MMS, surgical mapping is used during resection of the tumor: the surgeon removes the lesion, directly followed by 100% histological evaluation of the tumor margins on frozen sections, in contrast to standard excision, in which only a small portion of the margins are evaluated (2). Although MMS is beneficial for precise margin assessment, it is time consuming and labor-intensive. The preparation usually takes 20 to 60 minutes per excision, during which the patient waits, and the entire cycle is repeated until a tumor free plane resection margin is achieved (3). Moreover, the size of the tumor limits the indication for MMS. There is need for an instrument that can reliably support tumor excision with 100% margin control in a *real-time* manner, irrespectively to the size and origin of the tumor.
Molecular imaging using targeted near-infrared (NIR) optical contrast agents is a promising technique to accommodate this need. Epidermal Growth Factor Receptor (EGFR) is overexpressed in cSCC and has successfully been used as target for molecular imaging, particularly for assessment for tumor margins in head and neck squamous cell carcinoma (NCT03134846, the ICON study, UMCG).

Study objective

The main purpose of this pilot study is to investigate the feasibility of fluorescence imaging using cetuximab-IRDye800CW for intraoperative margin assessment in patients with cutaneous squamous cell carcinoma.

Study design

The current study is a single center, prospective, cross-sectional, phase I feasibility study. Ten patients with cSCC will be included. Two to four days prior to surgery, patients are administered with a predose of 75 mg *cold* cetuximab and 15 mg of the fluorescent tracercetuximab-IRDye800CW intravenously. After inclusion five patients, an interim analysis is performed to determine if a tumor-to-background ratio of >2 is obtained by either intraoperative fluorescence in vivo imaging or ex vivo fluorescence imaging. If

a TBR of >2 is found, inclusion will be continued to ten patients. If not, the dose is adjusted to a predose of 75 mg cetuximab and 25 mg of the fluorescent tracer cetuximab-IRDye800CW and ten more patients are included.

Intervention

Patients will * after written informed consent * receive an intravenous injection of the predose unlabeled cetuximab (after clemastine administration) and one hour later the fluorescent tracer Cetuximab-IRDye800CW. Two to four days later, fluorescence imaging is performed during surgery and directly after surgery, at the department of Pathology. Furthermore, fluorescence will be quantified by MDSFR/SFF spectroscopy. If the tumor location allows for plain imaging with our imaging probe, optoacoustic imaging will be performed prior to tumor resection.

Study burden and risks

Burden:
The burden associated with participation consists of one extra visit to the hospital for tracer administration, which will take approximately 2 hours. Also the surgical procedure and time under general anaesthesia will be prolonged with approximately 15-30 minutes for taking fluorescence images and spectroscopy measurements. If optoacoustic imaging is performed, this will take 5 minutes maximum.

Risks:
Risks to study participants are mainly related to the, already present, risks of the surgical procedure and to the administration of the tracer. No preclinical or clinical study reported higher than grade 2 adverse events, moreover, these studies used significant higher doses of the investigational product. Previous studies with cetuximab-IRDye800CW reported no tracer related serious events. Currently, a phase 1-2 trial is performed at the UMCG with Cetuximab-IRDye800 (NCT03134846), no tracer related serious advents were reported so far.

Benefit:
Patients will have no benefit from this study directly. Surgery will be planned as usual. During surgery, no decisions will be made based on the fluorescence imaging.

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) Biopsy confirmed diagnosis of cSCC and scheduled to undergo surgical resection;
2) Age * 18 years;
3) Written informed consent;
4) Mentally competent person showing adequate potential for follow-up; For female subjects who are of childbearing potential, are premenopausal with intact reproductive organs or are less than 2 years post-menopausal:
5) A negative serum or urine pregnancy test prior to receiving the tracer.
6) Willing to ensure that she or her partner uses effective contraception during the trial and for 6 months thereafter.

Exclusion criteria

1) Medical or psychiatric conditions that compromise the patient*s ability to give informed consent;
2) Concurrent uncontrolled medical conditions.
3) Received an investigational drug within 30 days prior to the dose of

cetuximab-IRDye800CW;
4) Tumors at sites of which the surgeon would assess that in vivo imaging would not be feasible;
5) Had within 6 months prior to enrollment: myocardial infarction, cerebrovascular accident, uncontrolled cardiac heart failure, significant liver disease, unstable angina;
6) Inadequately controlled hypertension with or without current antihypertensive medications;
7) History of infusion reactions to cetuximab or other monoclonal antibody therapies
8) Evidence of QT prolongation on pretreatment ECG (greater than 440 ms in males or greater than 450 ms in females);
9) Patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents;
10) Magnesium, potassium and calcium deviations that might lead to cardiac rhythm (grade II or higher deviations by CTCAE).
11) Life expectancy < 26 weeks;
12) Karnofsky performance status < 70%.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-07-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	MSOT
Registration:	No

Product type:	Medicine
Brand name:	cetuximab
Generic name:	cetuximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	cetuximab-800CW
Generic name:	cetuximab-800CW

Ethics review

Approved WMO Date:	01-04-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-05-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-07-2020
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
EudraCT	EUCTR2017-002249-31-NL
CCMO	NL69222.042.19