# Real-time margin assessment in head and neck cancer - enhancing specificity by combining fresh frozen sectioning with targeted fluorescence imaging The LIGHTNING study

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Soft tissue neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON51847

**Source**
ToetsingOnline

**Brief title**
Lightning study

### Condition

- Soft tissue neoplasms malignant and unspecified

**Synonym**
Head and neck cancer, oral squamous cell carcinoma

**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:** Fluorescence Imaging, Head and Neck Cancer Surgery, Margin assessment

## Outcome measures

### Primary outcome

- Macroscopic fluorescent signals on the excised tissue specimen and tracer distribution observed with fluorescence imaging;

- Detection rates of tumor-positive margins and close margins using fluorescence imaging and FFS;

- Number of additional resections based on the obtained fluorescent imaging and FFS data.

### Secondary outcome

- Patient characteristics (age, sex, BMI, history and morbidity, localization of primary tumor and lymph node metastasis, vital parameters and presence of symptoms before and after tracer administration);

- Feasibility of on-site, intra-operative, tissue analysis by both surgeon and pathologist.

- Feasibility of novel 3D imaging methods of the obtained additional biopsies (if clinical feasible) and correlation with standard histopathology

# Study description

### Background summary

Surgery remains one of the main pillars in the treatment of head and neck cancer. Margin status is the most important predictor of local tumor control in surgically treated head and neck cancer and determines postoperative treatment. A margin of <1 mm of normal tissue is considered a positive margin and requires reoperation or postoperative chemoradiation with a combination of cisplatin and 5FU, which substantially increase morbidity. Margins wider than 1 mm require re-operation or, if that is not possible, post-operative radiotherapy without the concomitant use of chemotherapy. This causes fewer side effects than radiation with chemotherapy. Currently, no technology is available in the operating room that reliably supports the surgeon during tumor excision to assess the status margin. In fact, surgeons can only combine preoperative imaging data with tactile and visual information during surgery to assess tumor margins with limited accuracy. With the introduction of molecular imaging techniques using near-infrared (NIR) fluorescent optical contrast agents coupled to monoclonal antibodies, new avenues have been opened for intraoperative assessment of tumor boundaries. These tracers are based on antibodies directed against epidermal growth factor receptor, i.e. cetuximabIRDye800CW, in patients with head and neck cancer. Initial studies have shown that systemic administration of these compounds is safe and tumor specific. Phase I studies, performed at the UMCG, among others, show promising results with regard to intraoperative margin determination. These findings are the reason to further investigate this innovative application, with the focus on improving specificity and making it directly clinically applicable. . In other words, to be able to act immediately on the basis of the gathered results. The research is subsidized by the UMCG, in the context of a Mandema Stipendium, which is awarded to young researchers (Dr. F.J. Voskuil).

## Study objective

The main aim is to test whether cetuximab-IRDye800CW is a reliable marker for residual tumor remnants in resection margins after surgical removal of head and neck cancer. To increase the specificity of cetuximab-800CW, a specific frozen section can be taken peroperatively, based on the fluorescence, in consultation between the surgeon and pathologist.
The aim is to improve the positive predictive value of cetuximab-IRDye800CW fluorescence as a marker for a tumor positive resection margin.

## Study design

The study is designed as a follow-up phase 2 study, a prospective cross-sectional diagnostic study in patients with head and neck cancer requiring surgical excision.
This study is a follow-up to an already performed study in which patients with head and neck cancer (n=80) were administered the fluorescent substance cetuximab-800CW, and the optimal dose of this substance was determined (75mg cetuximab followed by 15mg cetuximab-800CW). ). This study showed that

cetuximab-800CW has an excellent sensitivity for cancer detection in the margin, but the specificity can still be improved. The present study attempts to improve this by specifically taking a frozen section of the margin on the excised tissue specimen, based on the fluorescence imaging. Based on this finding, an additional resection can be performed immediately if deemed useful and safe by the surgeon. This follow-up study will serve as a prelude to a multicenter phase III study. In the current study 20 patients will be included.

**Intervention**

Tracer administration: patients visit the hospital 2 days prior to their scheduled surgery for their head and neck tumor.
The cetuximab-IRDye800CW will be injected by slow infusion and patients will be monitored for potential
effects. Patients receive unlabeled dose of cetuximab (75mg) 1 hour prior to 15mg
Received cetuximab-irdy800cw. Before cetuximab administration, 2mg clemastine will be administered, according to standard protocol cetuximab administration in the UMCG.

If, on the basis of fluorescence imaging and/or frozen section determination, it is considered useful and safe to perform a direct resection in order to achieve a wide margin, this can be performed peroperatively.

**Study burden and risks**

Burden - Time investment: Patients have to make an extra visit to the UMCG, two days before their planned surgery, which takes about 2-3 hours. Usually patients are admitted one day before the scheduled surgery. Burden of additional procedures: 1) Intravenous administration of cetuximab-IRDye800CW and cetuximab. 2) Estimated time for taking fluorescence images is approximately 10-15min. However, the surgery often does not have to wait for this, as other actions can be performed while performing imaging of the excised tissue. Therefore, the time under general anesthesia might be prololonged with 10-15minutes. The usual time of surgical procedures to remove head and neck tumors ranges from 2 hours to 15 hours, depending on the complexity of the surgical procedure. 3) If fluorescence is observed in the resection specimen, re-resection will be considered if deemed safe by surgeon. Risks: Allergic reactions to cetuximab have been reported, but this is considered a low risk Benefit: Patients may benefit directly from this study. The operation will be scheduled as usual. If fluorescence is observed in the resection specimen, re-resection will be considered if deemed safe by surgeon. The results of this type of research may benefit other patients with cancer in the future. Clinical experience will be gained with fluorescent labeled antibody to assess margin during head and neck cancer surgery.

# 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

- Cytology and/or histology-confirmed diagnosis of oral squamous cell carcinoma and scheduled to undergo surgical removal as decided by the multidisciplinary head and neck tumor board of the UMCG;
- Age >= 18 years;
- Written informed consent.

## Exclusion criteria

- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent;
- Concurrent uncontrolled medical conditions;

- Participated in a clinical trial in which an investigational drug was administrated within 30 days prior to the dose of cetuximab-800CW;
- History of myocardial infarction, cerebrovascular accident, uncontrolled cardiac heart failure, significant liver disease (ALT >3X upper limits of normal or increased total bilirubin) or unstable angina within 6 months prior to enrollment;
- Inadequately controlled hypertension with or without current antihypertensive medications;
- History of allergy or infusion reactions cetuximab or other monoclonal antibody therapies;
- Pregnant or lactating women. Documentation of a negative pregnancy test must be available for women of childbearing potential. Moreover, the need to be willing to ensure that she or her partner uses effective contraception during the trial and for 6 months thereafter. 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.
- Life expectancy < 12 weeks;

# Study design

## Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-01-2023 |
| Enrollment: | 20 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Cetuximab |
| Generic name: | Cetuximab |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Cetuximab-IRDye800CW |
| Generic name: | Cetuximab-IRDye800CW |

## Ethics review

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|---|---|
| Approved WMO Date: | 13-10-2022 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 06-02-2023 |
| Application type: | First submission |
| 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 | EUCTR2022-002779-12-NL |

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT05499065 |
| CCMO | NL81321.042.22 |