# Prognostic and predictive value of 18F-fluoroazomycin arabinoside-PET/CT in head and neck squamous cell carcinoma

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2 Objectives2.1 Primary objective •To evaluate FAZA-PET/CT as a prognostic factor of the loco-regional control rate at 2 years in HNSCC patients receiving chemo-radiotherapy ± nimorazole.•Time to locoregional recurrence is counted from the day of...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Miscellaneous and site unspecified neoplasms malignant and unspecified |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON43404

**Source**
ToetsingOnline

**Brief title**
18F-FAZA-PET/CT in head and neck cacer

### Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

**Synonym**
squamous cell carcinoma of the head and neck; head and neck cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** St. Luc University Hospital; Université Catholique de Louvain
**Source(s) of monetary or material Support:** Ministerie van OC&W,European Organisation

for Reasearch and Treatment of Cancer (EORTC)

## Intervention

**Keyword:** 18F-fluoroazomycin arabinoside-PET/CT, chemoradiotherapy, head and neck cancer, hypoxia

## Outcome measures

### Primary outcome

•To evaluate FAZA-PET/CT parameters as prognostic factors for the loco-regional control rate at 2 years in HNSCC patients receiving chemo-radiotherapy ± nimorazole.

•Time to locoregional recurrence is counted from the day of randomization to the day of the first record of local or regional progression. Distant recurrence, second cancer and death in absence of locoregional recurrence are not considered events of interest.

The PET / CT scans objective parameters for hypoxia will be determined within the primary tumor and the pathologic nodes, based on standardized uptake values (SUV), for example: SUVmax, SUVmean, total hypoxic volume x SUVmean.

Definition of hypoxia within a tumor on FAZA PET/CT:

A hypoxic voxel will be defined as a voxel expressing a SUV equal or above the SUVmean of the posterior contralateral neck muscles plus three standard deviations (Servagi-Vernat S, et al. A prospective clinical study of $^{1}$*F-FAZA PET-CT hypoxia imaging in head and neck squamous cell carcinoma before and during radiation therapy. Eur J Nucl Med Mol Imaging. 2014 Aug;41(8):1544-52.).

**Secondary outcome**

•To evaluate the change in FAZA uptake at day 14 (14 days after starting chemo-radiotherapy treatment relative to baseline), against patient*s outcome measured by loco-regional control rate at 2 years.

•To investigate the agreement between FAZA uptake and 15 gene signatures.

Definition of response or non-response by repeated scans (pre-/during treatment):

In the patients with tumors having a hypoxic volume at baseline, a threshold of hypoxic volume change will be explored to define the response or non-response, based on patient outcomes (loco-regional control rate at year 2).

# Study description

**Background summary**

1. Background of the study

1.1 Hypoxia and radio-responsiveness
Hypoxia, a condition of insufficient O2 to support metabolism, could occur when a tumor outgrows its vascular supply. Hypoxia is a cause of resistance to radiotherapy, especially in patients with head and neck squamous cell carcinoma (HNSCC). Modification of tumor hypoxia improves loco-regional control and survival in patients with HNSCC treated with radiotherapy (Overgaard J, 2011). In particular, the concomitant use of nimorazole, an hypoxic cell sensitizer, has been demonstrated by DAHANCA to significantly improve outcome in patients with HNSCC (Overgaard J, 1998). However, such study was conducted in patients treated by radiotherapy alone, and the benefit of hypoxic cell sensitizer in HNSCC patients treated by concomitant chemo-radiotherapy is still unknown. As a consequence, this treatment regimen has never been adopted outside of Denmark. And one can hypothesize that only patients with hypoxic tumors will respond to hypoxic cell radiosensitizer. In this respect, a 15-gene hypoxia classifier has been recently identified and tested retrospectively in the 323 patients included in the DAHANCA study mentioned above (Toustrup K, 2011). The

classifier has been demonstrated to be an efficient tool to categorize tumors for their hypoxic status and therefore responsiveness to combination treatment with radiation and hypoxic modifier.
In this framework, DAHANCA and EORTC have decided to join forces to conduct a blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of HPV/p16 negative squamous cell carcinoma of the head and neck (EORTC 1219 trial). The objectives of this trial are 1) to confirm on a multicentric basis that the hypoxic cell radiosensitizer nimorazole can improve the effect of primary chemo-radiotherapy in patients with locally advanced HNSCC, and 2) to demonstrate that patients who benefit from such combination can be predicted by the use of a hypoxic gene profile. This study will be conducted in European, Canadian and Australian centers. A total of 640 patients will be required to demonstrate a 12% improvement (from 65 to 77%) in loco-regional control rate at 3 years in the whole patient population, and of 22% (from 52 to 74%) in the patients with hypoxic tumors.

1.2 Imaging detection of tumor hypoxia
The use of multimodality imaging has rapidly developed to assess tumor microenvironment characteristics, including tumor cell hypoxia and tumor perfusion status.
Various hypoxia specific tracers have been tested clinically, mainly based on nitroimidazoles. Nitroimidazoles are reduced under hypoxia and become bound to cell components in hypoxic cells only (Haubner R, 2010). The first tracer to be tested clinically was 18F-flouromisonidazole (FMISO), and it is still widely used (Koh WJ, et al., 1992; Rajendran JG, et al., 2006; Mortensen LS, et al., 2010). The novel hypoxia specific tracer 18F-fluoroazomycin arabinoside (FAZA) has generated higher tumor-to-background ratios compared to FMISO in preclinical studies (Piert M, et al., 2005; Reischl G, et al., 2007). FAZA also becomes a more attractive tracer for clinical use, due to its more rapid clearance of unbound tracer from non-hypoxic tissues (Piert M, et al., 2005).
In some clinical studies, FAZA-PET/CT imaging has been proved as a suitable assay with prognostic potential for detection of hypoxia in HNSCC (Mortensen LS, et al., 2012). In the DAHANCA-24 study, a significant difference in disease free survival rate during a median follow up of 19 months was detected between patients with non-hypoxic tumors (93%) and with hypoxic tumors (60%). Meanwhile, the corresponding 30-month loco-regional control values showed also a trend toward significant difference (P=0.07) in hypoxic and non-hypoxic tumor (Mortensen LS, et al., 2012). The consistent results were also reported by FMISO studies, positive FMISO taken at 2 hours (Rischin D, et al., 2006; Dirix P, et al., 2009) and 4 hours (Eschmann SM, et al., 2005) after injection before starting chemo-radiation were at an increased risk of loco-regional relapse.

In the framework of the EORTC 1219 study, the aim of this sub-study is to explore the prognostic and predictive values of FAZA-PET/CT, and to investigate the correlations between various biomarkers.

References:
Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck - a systematic review and meta-analysis. Radiother Oncol 2011;100:22-32

Overgaard J, Hansen HS, Overgaard M, Bastholt L, Berthelsen A, Specht L, Lindeløv B, Jørgensen K. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol. 1998 Feb;46(2):135-46.

Toustrup K, Sørensen BS, Nordsmark M, Busk M, Wiuf C, Alsner J, Overgaard J. Development of a hypoxia gene expression classifier with predictive impact for hypoxic modification of radiotherapy in head and neck cancer. Cancer Res. 2011 Sep 1;71(17):5923-31.

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Koh WJ, Rasey JS, Evans ML, et al. Imaging of hypoxia in human tumors with [F-18]fluoromisonidazole. Int J Radiat Oncol Biol Phys 1992;22:199-212.

Rajendran JG, Schwartz DL, O*Sullivan J, et al. Tumor hypoxia imaging with [F-18]fluoromisonidazole positron emission tomography in head and neck cancer. Clin Cancer Res 2006;12:5435-41.

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Piert M, Machulla HJ, Picchio M, et al. Hypoxia-specific tumor imaging with 18F-fluoroazomycin arabinoside. J Nucl Med 2005;46:106-13.

Reischl G, Dorow DS, Cullinane C, et al. Imaging of tumor hypoxia with [124I] IAZA in comparison with [18F] FMISO and [18F]FAZA - first small animal PET results. J Pharm Pharm Sci 2007;10:203-11.

Mortensen LS, Johansen J, Kallehauge J et al., FAZA PET/CT hypoxia imaging in patients with squamous cell carcinoma of the head and neck treated with radiotherapy: Results from the DAHANCA 24 trial. Radiother Oncol. 2012 Oct;105(1):14-20.

Rischin D, Hicks RJ, Fisher R, et al: Prognostic significance of [18F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: A substudy of Trans-Tasman Radiation Oncology Group study 98.02. J Clin Oncol 24:2098-2104, 2006.

Dirix P, Vandecaveye V, De Keyzer F, et al: Dose painting in radiotherapy for head and neck squamous cell carcinoma: Value of repeated functional imaging with (18)F-FDG PET, (18)F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI.J Nucl Med 50:1020-1027, 2009.

Eschmann SM, Paulsen F, Reimold M, et al: Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. J Nucl Med 46:253-260, 2005.

## Study objective

2 Objectives

2.1 Primary objective
•To evaluate FAZA-PET/CT as a prognostic factor of the loco-regional control rate at 2 years in HNSCC patients receiving chemo-radiotherapy ± nimorazole.
•Time to locoregional recurrence is counted from the day of randomization to the day of the first record of local or regional progression. Distant recurrence, second cancer and death in absence of locoregional recurrence are not considered events of interest. The follow-up will be done regularly according to a well-defined agenda.

2.2 Secondary objectives
•To evaluate the change in FAZA uptake at day 14 (14 days after starting chemo-radiotherapy treatment relative to baseline), against patient*s outcome measured by loco-regional control rate at 2 years.
•To investigate the agreement between FAZA uptake and 15 gene signatures.

## Study design

A subgroup of eligible patients scheduled to receive chemo-radiotherapy in the EORTC 1219 study will be prospectively enrolled before the first treatment into the imaging sub-study aiming to evaluate FAZA-PET/CT imaging as a prognostic factor.
Patients participating to the imaging sub-study will follow the same protocol treatment as the other patients of EORTC 1219 trial with the same clinical evaluations. However, they will have two additional imaging examinations: one FAZA-PET/CT scan at baseline (within one week before start of chemo-radiotherapy treatment) and one early FAZA-PET/CT scan at day ±14 with a fixed schedule.

## Study burden and risks

Patients will undergo two extra scans before and during treatment with chemo-radiotherapy ± nimorazole. 18F-FAZA will be injected intravenously before each scan; this will not cause extra radiation burden for the patients

undergoing radiotherapy. Patients may develope an allergic reaction to the injected radiofarmacon (attributes). Patients will invest 3 hours of time for each scan. The scans will be planned on days that patients have to visit the hospital for other purposes, as much as possible. The second scan will always be planned on a day that the patient will be in hospital for radiotherapy. Patients will have no personal benefit from participation in the study.

## 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

•Patients randomized in any of the two arms of EORTC 1219 trial
•No contraindication to FAZA-PET/CT: pregnant or breast-feeding woman; for woman subject of childbearing potential, a pregnancy test will be done within 72 hours before the examination.

•Patients must be scanned on a PET/CT scanner accredited, and in compliance with the provided imaging guidelines.
•Biopsy must be performed 2 weeks before imaging scans.
•Patient must have given written informed consent to participate to the imaging sub-study.
Additional eligibility criteria for the imaging sub-study
•Delay between the baseline scan (FAZA-PET/CT) and the start of the radiotherapy < 7 days.
•Patients with at least one measurable lesion at baseline defined as a lesion larger than 2 cm in diameter.;Inclusion criteria EORTC 1219 trial:
* Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations
* Newly diagnosed tumors classified as stage III-IV located in the larynx, oropharynx and hypopharynx
* HPV/p16 negative
* Histopathological diagnosis of invasive squamous cell carcinoma in the primary tumor.
* No distant metastasis (M0).
* Age >= 18 years.
* Tumor material available for central testing of the hypoxic gene signature
* WHO performance 0-2.
* All hematology and biochemical investigations, should be done within 4 weeks before randomization (maximum 6 weeks before treatment starts)
* Normal bone marrow function based on routine blood samples, i.e. neutrophils >= 1.0 x 109/L, platelets >= 75 x 109/L, hemoglobin >= 10.0 g/dL or 6.2 mmol/L
* Normal kidney function creatinine clearance >= 60 mL/min, and Electrolyte balance: calcium <= 11.5 mg/dl or 2.9 mmol/L, magnesium >= 1.2 mg/dl or 0.5 mmol/L
* Normal liver function assessed by routine laboratory examinations, i.e. bilirubin < 1.5 x ULN, ALT< 3 x ULN, alkaline phosphatases < 3 x ULN
* No prior or current anticancer treatment to the head and neck area (e.g. radical attempted or tumor reductive surgery, neo-adjuvant chemotherapy, EGFR inhibitors or radiotherapy).
* Patients must be candidate for curative intent external beam chemo-radiotherapy, and must be expected to complete the treatment.
* All patients should have an oral and dental examination including preferably clinical and radiological examination. Whenever indicated, extraction of dental elements should be carried out at least 10 to 14 days before treatment start.
* Radiotherapy planned to start within acceptable delay (preferably within 2 weeks and a maximum of 4 weeks from randomization).
* Radiotherapy planned to start within 8 weeks from baseline imaging tumor assessment.
* Patients should not have symptoms of peripheral neuropathy, assessed by medical history.
* Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial.
* All subjects must:
* Agree to abstain from donating blood while receiving therapy and for four weeks following discontinuation of therapy.
* Agree not to share study medication with another person and to return all unused study drug to the investigator.

## Exclusion criteria

The same as the EORTC 1219 trial:
* Patients who have received treatment with any investigational drug substance within 4 weeks prior to randomization.
* Current participation in any other interventional clinical study.
* Pregnant or breast-feeding female patient. Pregnancy test should be done within 72 hours from treatment start.
* Female subjects of childbearing potential (defined as a sexually mature woman who 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally post-menopausal (amenorrhoea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months)) not willing to use adequate contraception during study and for 6 month after last dose of study drug.
* Male subjects not willing to use condoms throughout study drug therapy, and for 6 months after cessation of study therapy if their partner is of childbearing potential and has no contraception.
* Known or suspected HIV infection.
* Second malignancies in the 3 years prior to study entry with the exception of surgically cured carcinoma in situ of the cervix, in situ breast cancer, incidental finding of stage T1a or T1b prostate cancer, and basal/squamous cell carcinoma of the skin.
* Uncontrolled or chronic bacterial, fungal or viral infection.
* Known or suspected hypersensitivity to component(s) of investigational product or cisplatin contraindication.

# Study design

## Design

**Study type:** Observational invasive

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 28-03-2017 |
| Enrollment: | 60 |

| | |
|---|---|
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | 18F-fluoroazomycin arabinoside |
| Generic name: | 18F-fluoroazomycin arabinoside |
| Product type: | Medicine |
| Brand name: | Cisplatin |
| Generic name: | Cisplatin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Nimoral |
| Generic name: | nimorazole |

## Ethics review

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|---|---|
| Approved WMO Date: | 09-05-2016 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 29-11-2016 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

## 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 | EUCTR2015-005278-40-NL |
| CCMO | NL55752.091.15 |