FDG-PET/CT to reduce the need for sentinel lymph node biopsy in early-stage oral cancer.

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In this study, we aim to investigate the possibility of FDG-PET/CT to reduce the number of (positive) SLNB procedures in patients with early stage oral squamous cell carcinoma and a clinically negative neck.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Observational invasive

Summary

ID

NL-OMON53440

Source
ToetsingOnline

Brief title
PETN0

Condition

- Metastases

Synonym
oral cancer, Oral squamous cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF

Intervention

Keyword: FDG-PET/CT, Head and Neck squamous cell carcinoma, Oral cancer, Sentinel lymph node biopsy

Outcome measures

Primary outcome

The primary objective of this study is to reduce the need for SLNB by

FDG-PET/CT in cN0 OSCC patients.

Secondary outcome

• To optimize scoring criteria for the detection of (occult) lymph node

metastases by FDG-PET/CT with a high positive predictive value.

• To assess the sensitivity, specificity, PPV, negative predictive value and

accuracy for the different scoring criteria.

• To investigate inter-observer agreement before and after scoring criteria are

established.

• To compare the quality of life and costs in three different diagnostic

scenarios 1) PET/CT, 2) SLNB, and 3) PET/CT and, only if negative, SLNB.

• To obtain insight into patients* preferences and experience of the diagnostic

procedures.

Study description

Background summary

In the Netherlands 3017 patients were diagnosed with head and neck squamous cell carcinoma (HNSCC) in 2020, of whom 920 had oral squamous cell carcinoma (OSCC). In HNSCC the detection of lymph node metastases (LNM) is highly important because adequate treatment of the neck, i.e. neck dissection and/or radiotherapy is available. Sentinel lymph node biopsy (SLNB) can reliably

detect occult LNM in early-stage (cT1-2N0) OSCC and is now incorporated in many national guidelines. Management of the neck based on SLNB has some limitations. SLNB remains an invasive surgical procedure with associated morbidity. An eventual subsequent completed neck dissection (CND) is a second stage procedure in 30% of patients and should proceed in a timely fashion, which may be a logistic problem. Moreover, subsequent CND is more challenging than elective neck dissection (END) and harbours a higher risk of complications.

Although promising results have been reported, the role of FDG-PET/CT to detect occult LNM in HNSCC patients is unclear. Studies are difficult to compare: different scan protocols, definitions of the N0 neck, criteria for PET positivity, ways of reading scans, and reference standards have been used. Routine histopathological examination of neck dissection specimens can miss micrometastases, whereas step serial sectioning and immunohistochemistry (as performed in SLNB) can increase the yield by as much as 15.2%. Therefore, the most reliable reference standard, which has not been used in PET/CT studies before, is SLNB and follow-up without treatment of the neck in case of negative SLNB. Since PET imaging has improved considerably due to technical advances enabling integration of PET and CT devices, improvements in detector capabilities yielding higher image resolution, and optimization of head and neck acquisition parameters, prospective studies are needed.

The number of SLNB procedures and second stage CND can be reduced by performing direct neck dissection without SLNB procedures in patients in whom occult LNM can be predicted with very high positive predictive value (PPV) by FDG-PET/CT. By varying cut-off levels scoring criteria can be developed and optimized to predict the presence of lymph node metastases with high PPV instead of high sensitivity, which is usually done. When focused on high PPV the sensitivity will probably be lower, but missed LNM will then be detected by SLNB when performed after negative FDG-PET/CT.

Study objective

In this study, we aim to investigate the possibility of FDG-PET/CT to reduce the number of (positive) SLNB procedures in patients with early stage oral squamous cell carcinoma and a clinically negative neck.

Study design

This study is designed as a prospective Dutch multicenter cohort study. A total of 159 patients with early-stage OSCC (cT1-3, cN0, M0), scheduled for transoral tumor resection and SLNB, will be included in a multicenter study to evaluate the potential reduction of SLNB procedures using newly developed FDG-PET/CT scoring criteria and assess the diagnostic accuracy of FDG-PET/CT for the detection of cervical lymph node metastasis in cN0 OSCC patients with and without use of these scoring criteria.

Patients with early-stage oral cavity carcinoma (cT1-3, cN0, M0; tumor location will be limited to the intraoral areas of mucosal lip, buccal mucosa, lower alveolar ridge, upper alveolar ridge, retromolar gingiva, retromolar trigone, floor-of-the-mouth, hard palate, and the mobile portion of the oral tongue) scheduled for transoral tumor resection with SLNB will be asked to participate in the study.

After informed consent is obtained each included patient will undergo FDG-PET/CT and SLNB within a maximum of 3 weeks. It is likely that the majority of the cases, the SLNB and FDG-PET/CT can be performed within a one-week timeframe. Efforts will be made to achieve this timeframe.

The PET/CT will be acquired using dedicated EANM Research Ltd. (EARL2) accredited PET/CT systems. Patient preparation, scanner calibration, image acquisition, and reconstruction will be performed according to EANM standards. After a fasting period of at least 6 hours, patients receive an intravenous injection of FDG. Approximately 60 min after the administration of the tracer a PET-low dose CT of the head and neck and chest (arms down) are acquired. After the PET-low dose CT a contrast-enhanced CT of the head and neck will be performed. When the patient has had a previous allergic reaction after administration of contrast fluid, only a PET-low dose CT of the head and neck and chest is sufficient for participating in this study and a contrast-enhanced CT will not be performed. To avoid false-positive results by cytological puncture, PET/CT has to be performed before ultrasound-guided fine needle aspiration cytology (USgFNAC). Patients with positive USgFNAC will be excluded for further analysis since the neck is not clinically negative. With a prevalence of 27% and a sensitivity of 15.4%, it is expected that 4.2% of patients will have to be excluded for this reason.

The results of the PET/CT scan will not be used to alter surgical planning. Institutional nuclear physicians will score the PET/CT scan on potential other tumor sites in the thorax and upper abdomen. Relevant findings will be reported to the referring physician (e.g. infection or secondary malignancy in the lungs). After the SLNB each PET/CT scan will be individually scored by a panel of 5 experienced nuclear physicians without specific guidelines. The SLNB will be blinded for the PET/CT scan. All nodes with increased FDG uptake are scored as definitely positive, probably positive, equivocal, or probably negative. If a discrepancy occurs, adjudication will be conducted by a third nuclear physician. These results will be compared with the SLNB results and follow-up as the reference standard.

On histopathological examination of the neck dissection specimen efforts should be made to identify FDG-positive nodes and examine these similar to sentinel nodes. If no neck dissection is performed, the neck will be observed to see of eventually missed metastases become clinically manifest.

The SLNB procedure will be performed according to the practical and consensus

guidelines. Patients will undergo lymphoscintigraphy (including SPECT-CT) after peritumoral injection of [99mTc]Tc-nanocolloid(-ICG), the day before surgery or the day of surgery. Patients with a positive SLNB will undergo a neck dissection. In case of a negative SLNB patients are observed during follow-up according to the national guidelines.

Follow-up will be at least 12 months after SLNB to allow missed occult lymph node metastases to become clinically detectable. It is expected that 80% of the missed lymph node metastases (false negative) will become manifest in the first 12 months. Although not included in this research project (because of time limitations), included patients will be asked for participation in a long-term follow-up study, with at least two years follow-up, to assess late regional recurrences and improve the reference standard even further.

In addition, to gain insight into the patients* preferences and experience with diagnostic modalities, semi-structured interviews will be conducted with patients at the University Medical Center Utrecht and until data saturation has been reached..

Study burden and risks

Patients will undergo additional FDG-PET/CT before treatment. The SNLB procedure is standard care for these patients in the participating centers. Early-stage OSCC patients usually do not undergo FDG-PET/CT. FDG-PET/CT may detect other tumor sites. Patients may benefit from this, but false-positive findings may give a burden to the patients. This may include other additional examinations to confirm PET/CT findings. FDG-PET/CT is considered a safe procedure, with limited radiation exposure. Therefore, we conclude the risk is negligible for this study according to the NFU guidelines.

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

To be eligible to participate in this study, a subject must meet all of the following criteria:
• Newly diagnosed early-stage OSCC is defined as clinically T1-3, N0 (only when T3 is assessed based on tumor dimensions of >2 cm and <=4 cm with DOI >10 mm)
• The patient is >=18 years of age at the time of consent.
• The patient has no palpable lymph nodes in the neck.
• Clinical nodal staging (cN0) has been confirmed by ultrasound, CT, and/or MRI if performed (not mandatory).
• The patient is a candidate for transoral excision and SLNB.
• The patient has provided written informed consent authorization before participating in the study.
• Patients with prior malignancy of the head and neck area are allowed, provided the
patient meets both of the following criteria:
a. Underwent potentially curative therapy for all prior head and neck malignancies
and is deemed low risk for recurrence; and
b. No head and neck malignancy for the past three years and no evidence of recurrence.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• The patient has other pathologies than squamous cell carcinoma;
• The patient has a history of treatment of the neck (neck dissection and/or radiotherapy);

• The patient has ultrasound guided fine needle aspiration cytology positive for lymph node metastasis;
• The patient has poorly controlled diabetes mellitus;
• The patient refused preoperative imaging workups.

A potential subject who meets the following criteria will only be excluded for the contrast-enhanced CT of the head and neck:
• The patient has had a previous allergic reaction after administration of contrast fluid.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-01-2024
Enrollment:	159
Type:	Actual

Ethics review

Approved WMO Date:	27-09-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-09-2024
Application type:	Amendment
Review commission:	METC NedMec

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	NL83442.041.22