Sentinel lymph node detection and staging in early-stage oral cancer using superparamagnetic iron oxide nanoparticles

Published: 22-08-2022
Last updated: 18-01-2025

We propose to use an alternative superparamagnetic tracer containing ironoxide, which can be detected with MRI and with a magnetic probe. The spatial resolution of MRI is superior to gamma camera detection. Moreover, there is no radiation exposure…

Ethical review	Approved WMO
Status	Pending
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON51639

Source
ToetsingOnline

Brief title
MAGNETICS

Condition

- Metastases
- Head and neck therapeutic procedures

Synonym
oral cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF Kankerbestrijding 14109

Intervention

Keyword: Iron Oxide Nanoparticles, Magnetic Resonance Imaging, Oral Squamous Cell Carcinoma, Sentinel Lymph Node Biopsy

Outcome measures

Primary outcome

The primary study parameter is the diagnostic accuracy, in terms of sensitivity and negative predictive value, of a complete magnetic SLNB procedure (SPIO peritumoral injections, preoperative SPIO-enhanced MRI and SLN harvesting using a magnetometer) and the additional value of the magnetic SLNB procedure to the radioactive (conventional) SLNB. Results of the complete magnetic SLNB will be evaluated and compared with the reference standard, i.e. histopathological examination of SLNs and complementary neck dissection specimens as well as 12 months follow-up.

False-negative SLNB outcomes of included patients will be scored. False-negative rates (false-negative/(false-negative + true-positive)) following each SLNB technique and the combination will be calculated and presented in percentages. If a positive SLN is missed by one of the techniques (but depicted by the other technique) this SLN is considered false-negative for this technique. Using the false-negative rates, the sensitivity (true-positive/(true-positive + false-negative)) and NPVs (true-negative/(true-negative + false-negative)) will be calculated accordingly

for each technique separately and combined.

Secondary outcome

Detection rate (in percentages) of SLN(s) with SPIO-enhanced MR lymphoscintigraphy as compared to conventional lymphoscintigraphy using 99mTc-nanocolloid with histopathology as the reference standard as well as 12 months follow-up.

The number of SLNs identified for each subject will be recorded, and summary statistics (mean, median, standard deviation, minimum, and maximum) on the number of SLNs will be displayed.

The pathological status of SLNs will be assessed on a per subject basis. The number and percentages of subjects who have at least one histopathological-positive SLN will be calculated.

Study description

Background summary

Sentinel lymph node biopsy (SLNB) is a diagnostic staging procedure that has been implemented as Dutch standard oncological care for several tumor types, including early-stage (cT1/2N0) oral squamous cell carcinoma (OSCC). An infamous limitation of the routine SLNB procedure arises in situations where sentinel lymph nodes (SLN) are located in close vicinity of the radioactive tracer injection site. In these cases, due to the limited resolution of the γ-camera and SPECT, the hotspot of the tracer injection site can hide adjacent SLNs, which consequently hampers discrimination between tracer injection site and SLNs. This shine-through phenomenon is particularly evident in floor-of-mouth (FOM) OSCC, resulting in a significantly lower accuracy of SLNB in FOM tumors (sensitivity 63%; NPV 90%) compared to other oral cavity subsites (sensitivity 86%; NPV

95%).
A lower accuracy for SLNB can result in abandonment of occult lymph node metastasis, by erroneously staging the neck as negative for metastases, which will inevitably develop into clinical manifestation of disease and consequently harbors a poor oncological prognosis.

Study objective

We propose to use an alternative superparamagnetic tracer containing ironoxide, which can be detected with MRI and with a magnetic probe. The spatial resolution of MRI is superior to gamma camera detection. Moreover, there is no radiation exposure and no dependency on complex radioisotope production and transport infrastructure with this alternative.
The non-inferiority of superparamagnetic compared to radioactive tracers has already been proven in breast cancer. It is not clear if results obtained in breast cancer can be translated to oral cancer, because of its complex lymphatic drainage pattern and higher lymphatic flow. Two studies showed that preoperative identification of SLNs in oral cancer patients with a magnetic tracer on MRI lymphography corresponded with radioisotope tracer identification on lymphoscintigraphy. A recent feasibility study showed that SLNs with superparamagnetic particles of ironoxide (SPIO) could be identified intraoperatively by means of a magnetic probe after peritumoral injections of these SPIO particles. In another recent study we confirmed the feasibility to detect SLNs with SPIO nanoparticles intraoperatively and optimized the protocol of preoperative MRI visualization and intraoperative
detection for tracer dose and interval between injection and imaging. Combining the results of both studies revealed a sensitivity of 80% (4/5) and a negative predictive value of 93% (14/15), using routine histopathological examination of the elective neck dissection specimen as reference standard. Of note, 42% (8/19) of these patients had OSCC located in the FOM.

Study design

This study is designed as a prospective Dutch multicenter cohort study. A total of 82 patients with early-stage OSCC (cT1-3N0M0), scheduled for transoral tumor resection and SLNB, will be included in a multicenter study to evaluate SPIO-enhanced MRI and intraoperative detection of magnetic particles by magnetometer for SLNB. Following inclusion, participants will undergo both conventional (standard) lymphoscintigraphy and SPECT-CT after peritumoral administration of [99mTc]-nanocolloid as well as SPIO-enhanced MRI after peritumoral administration of superparamagnetic iron oxide nanoparticles. Paired images of each patient (i.e. [99mTc]-nanocolloid lymphoscintigraphic images including SPECT-CT and SPIO nanoparticles MR images) will be evaluated with regard to similarity of depicted draining lymph node basins, number and location of SLNs and their histopathological outcome. During surgery SLNB will be first performed using the magnetometer (harvested SLNs will also be measured

by gamma probe) by surgeon A (blinded for lymphoscintigraphy results) and thereafter using the gamma probe for eventual remaining SLNs in the neck by surgeon B (lymphoscintigraphy report available and/or discussed with the nuclear physician).

Results of the complete magnetic SLNB will be evaluated and compared with the reference standard, i.e. histopathological examination of SLNs and complementary neck dissection specimens as well as 12 months follow-up. False-negative SLNB outcomes of included patients will be scored. Accordingly, the diagnostic accuracy (i.e. sensitivity, negative predictive value) of both sentinel node biopsy methods only and the combination will be calculated and compared. Intranodal appearance on SPIO-enhanced MRI will be correlated to detailed histopathological examinations of the resected SLN. Although not included in this research project, due to time limitations, included patients will be asked for participation in a long-term follow-up study, with at least two years follow-up.

Intervention

The study population will receive peritumoral injections of superparamagnetic iron oxide nanoparticles (SPIO) and afterwards a pre-operative MRI lymphography will be performed to locate the sentinel nodes. On the day of surgery, or the day before, pre-operative MRI lymphography will be performed. First, the sentinel node extirpation will be performed with the magnetometer (Sentimag). Afterwards, the surgery will proceed according to standard protocol.

Study burden and risks

Patients will undergo additional peritumoral injections (i.e. SPIO 0.4 mL) and MRI lymphography with an estimated duration of 30 minutes. Besides irritation or pain at the injection site, adverse reactions after injection of SPIO rarely occur. Besides, there is substantial experience in the use of SPIO in breast cancer. No interactions between 99mTc-radiotracers and SPIO that might harm the patient are known. Magnetic SLNB may result in harvesting additional SLNs, not detected by conventional radioactive SLNB. Resection of additional SLNs, expected mainly close to the injection site (generally in level I of the neck), may have complications, but are rare in this procedure. However, harvesting these SLNs, which can be missed by conventional lymphoscintigraphy and SPECT-CT (false-negative outcome), provides better staging of the nodal basin. Abandonment of occult lymph node metastasis, especially if this has therapeutic consequences in context of SLNB, will inevitably result in clinical manifestation of disease, resulting in more extensive treatment (more often modified radical neck dissection and adjuvant radiotherapy) and a worse oncological prognosis. A slight prolongation of operation room time is expected, however operation risks are practically not increased. 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

1. The patient has provided written informed consent authorization before participating in the study.
2. The patient has a diagnosis of primary oral squamous cell carcinoma that is anatomically located in: mucosal lip, buccal mucosa, lower alveolar ridge, upper alveolar ridge, retromolar gingival (retromolar trigone), floor-of-the-mouth, hard palate or oral (mobile) tongue, and is stage cT1-T2 and T3 (only when T3 is assessed based on tumor dimensions of >2 cm and <=4 cm with DOI >10 mm) (see Appendix 3: Tumor Nodal Metastasis (TNM) Staging).
3. Clinical nodal staging (cN0) has been confirmed by at least ultrasound, with in case of suspicious lymph nodes ultrasound guided fine-needle aspiration cytology, CT and/or MRI within 30 days of the SLNB procedure.
4. The patient is a candidate for transoral excision.

5. 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.
6. The patient is >=18 years of age at the time of consent.
7. The patient has an ECOG status of Grade 0 - 2 (see Appendix 4: Performance Status Criteria).

Exclusion criteria

1. The patient has a diagnosis of squamous cell carcinoma of the head and neck in the following anatomical areas: non-mobile base of the tongue, oropharynx, nasopharynx, hypopharynx, and larynx.
2. The patient has clinical or radiological evidence of metastatic cancer to the regional lymph nodes.
3. The patient has a history of neck dissection, or gross injury to the neck that would pre-clude reasonable surgical dissection for this trial, or radiotherapy to the neck.
4. The patient is incapacitated.
5. The patient has had an intolerance or hypersensitivity to iron or dextran compounds, Magtrace® or lidocaine.
6. The patient has an iron overload disease.
7. The patient has an active implantable device in the upper body.
8. The patient is known with claustrophobia, who are a consequence unable to undergo MR imaging.
9. The patient has a contra-indication for MR imaging (e.g. metal implant).
10. The patient is pregnant.
11. Participation will result in unacceptable delay regarding oncological treatment.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2022
Enrollment:	82
Type:	Anticipated

Medical products/devices used

Generic name:	SentiMag and Magtrace
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	22-08-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-07-2024
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	NL81165.041.22