Phase III study assessing the *best of* radiotherapy compared to the *best of* surgery (trans-oral surgery (TOS)) in patients with T1-T2, N0-N1 oropharyngeal, supraglottic carcinoma and with T1, N0 hypopharyngeal carcinoma

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The main objective of the study is to assess and compare the patient-reported swallowing function over the first year after randomization to either IMRT or TOS among patients with early stage OPSCC, SGSCC and HPSCC.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON54095

Source
ToetsingOnline

Brief title
EORTC-1420 "Best of Radiotherapy vs Best of Surgery"

Condition

- Miscellaneous and site unspecified neoplasms benign
- Head and neck therapeutic procedures

Synonym

Oropharygeal caricoma, supraglottic and hypopharyngeal carcinoma, throat cancer

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC

Intervention

Keyword: Oropharyngeal, Radiotherapy, supraglottic and hypopharyngeal squamous cell carcinoma, Trans-oral surgery

Outcome measures

Primary outcome

The primary endpoint of this study is the MDADI score reported by the patient

at 12 months after randomization.

• The MDADI scale is composed of 19 items: Emotional (6 questions), Functional

(5 questions), Physical (8 questions) and the total MDADI score ranges from 20

(extremely low functioning) to 100 (high functioning).

• The study is powered to test the treatment difference at the 12 months* time

point.

Secondary outcome

Patient-reported MDADI at 4.5, 6 and 9 months

• Response after study treatment (measured at 6 months after randomization)

• Recurrence-free survival after complete response (CR)

• Local, regional, loco-regional and distant tumor control after CR

• Overall, disease specific and event free survival

• Second cancer

• Functional and HRQOL measures (PSS-HN, 100 ml swallow test, feeding tube use,

EORTC QLQ-C30 and H&N43)

Other secondary endpoints involve these same evaluations up to 5 years.

In general, clinical evaluation, pan-endoscopy with biopsy if indicated,

imaging scans taken at 6 months after randomization and evaluation of the MDT

shall be performed during the treatment and follow-up periods to evaluate

recurrence or progression. In the Best of Study, methods and schedule of follow

up are based on the NCCN guidelines as of 2016.

Study description

Background summary

Oropharyngeal Squamous Cell Carcinoma (OPSCC) arises in the soft palate, tonsils, base of tongue, pharyngeal wall, and the vallecula. The oropharynx is the posterior continuation of the oral cavity extending from the palate superiorly to the level of hyoid bone inferiorly. It is subdivided into the:
• lateral wall: palatine tonsil, tonsillar fossae and pillars
• anterior wall: base of tongue and vallecula
• superior wall: soft palate and uvula
• posterior pharyngeal wall

It is a relatively uncommon malignancy with approximately 123,000 cases diagnosed worldwide each year and about 79,000 deaths. The incidence of OPSCC is rapidly increasing, associated with rising rates of oral infection with the human papillomavirus (HPV). Regardless the HPV status, early stage OPSCC has an average 5-year survival rate of over 80%. Most of the patients with early stage OPSCC are usually cured. Treatment of early stage OPSCC can be successfully achieved with primary surgery including neck dissection, as indicated, or with definitive radiotherapy.
Several retrospective studies have independently shown comparable oncologic outcomes from TOS as compared with external beam radiation. However, these studies rely on historical data affected by selection bias, even in matched cohort analysis. Nevertheless, disease specific survival (DSS) seems to be invariably comparable between the 2 treatment modalities. The most recent meta-analysis on early stage OPSCC reported a 5 years DSS of 90.4% (95% Confidence Interval (CI): 85.6 - 95.2%) in the radiotherapy group and 89.6% (95% CI: 81.8 - 97.3%) in the trans*oral surgery (TOS) group (Evidence Level Class IV). The quality of the studies was similar in both groups. Equivalent

prognostic rates were reported in other studies.
Moreover, a literature review has been recently published comparing trans*oral robotic surgery (TORS) with radiation therapy for T1 and T2 OPSCC. The analysis performed within this study suggests that TOS was as effective as radiotherapy for the treatment of early OPSCC in terms of oncological outcome (2-year overall survival ranged from 84% to 96% for Intensity-Modulated Radiation Therapy (IMRT) and from 82% to 94% for TORS).
Supra-glottic squamous cell cancer (SGSCC) is a second relatively uncommon malignancy. As opposed to OPSCC the percentage of HPV-positive disease in this location is negligible. According to current guidelines treatment for early stage (stage I and III) consists of either radiation therapy only or organ preservation surgery with similar oncological outcome ranging between 68% - 81% DSS at 5 years.
Finally, also hypopharyngeal cancer is a very rare disease. Current treatment guidelines recommend either surgery or radiation-only for T1 and T2 N0 cancers.
The current standard treatment for early stage OPSCC and SGSCC is therefore based on either surgery or radiotherapy, both associated with comparable, high tumor control rates but with different side effect profiles and technical constraints. Radiotherapy and surgery are thus currently considered equivalent based on similar cancer control rates so that treatment choice is center-dependent.
With the advancements in the field of head and neck cancers novel strategies have been developed that allow a more targeted approach to the cure of early stage OPSCC, and SGSCC. These techniques that have been developed in parallel in the RT and surgical fields have led to a significant reduction of treatment-related morbidity, whilst preserving excellent oncological control.
The choice between these two treatment options is generally based on the experience accumulated in each institution but not based on level 1 evidence. Only a prospective randomized trial will be able to answer the question about true functional equivalence of the two treatment modalities for these diseases and shed light onto the question, which one of the modalities will provide better functional outcome.
The trial will therefore identify a new standard of care for the majority of early-stage head and neck cancer based on the most optimal function preservation, whilst assuring an excellent oncological control rate as demonstrated by previous meta-analysis.

Study objective

The main objective of the study is to assess and compare the patient-reported swallowing function over the first year after randomization to either IMRT or TOS among patients with early stage OPSCC, SGSCC and HPSCC.

Study design

This is an open-label, investigator initiated, multicenter, randomized phase

III study assessing and comparing the swallowing function after surgery (TOS) versus radiotherapy (IMRT) in patients with early stage squamous cell carcinoma of the oropharynx, supraglottis and hypopharynx.

Intervention

Eligible patients will be randomized 1 to 1 to TOS (Arm 1) or IMRT (Arm 2), stratifying for tumor localization (lateral lesions: Lateral wall, tonsil, glosso-tonsillar sulcus, lateral piriform sinus; central lesions: base of tongue, vallecula, supraglottis, medial piriform sinus), N stage (T1/2N0 vs T1/T2N1), MDADI score at baseline (below and above 67.0 points) and country.

Study burden and risks

The present study compares two standard treatments, in which the swallowing function of patients is measured a few times more extensively by means of questionnaires.

The follow-up frequency proposed in the study compared to the regular oncological follow-up is not significantly higher than the frequency as proposed in the national guideline. Participants are asked to complete questionnaires, but the absolute burden of this is low.

Although the burden for the patients is manageable, the profit for patients is also relatively limited. No difference in survival is expected, for example. The questionnaires and the additional studies focus on the swallowing function. It is known that swallowing has a major impact on the quality of life. More accurate follow-up may lead to an earlier determination of a possible swallowing problem. Whatever makes it possible to do something about it.

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

OPSCC in one of the following sub-sites: base of tongue, lateral pharyngeal wall, tonsil, glosso-tonsillar sulcus, vallecula or SGSCC in one or more of the following sub-sites: epiglottis, aryepiglottic fold, false cord or HPSCC in one or more of the following subsites: Lateral and medial wall of piriform sinus (sub-sites are defined as lateral (lateral pharyngeal wall, tonsil, glosso-tonsillar sulcus, lateral wall of piriform sinus) vs. central lesions (base of tongue, vallecula, all supraglottic sites, medial wall of piriform sinus))
• TNM stage I-III (7th AJCC classification) for OPSCC and SGSCC: T1 or T2, N0 or T1 or T2, N1 with one single neck node <= 3cm without radiographic signs of extracapsular extension (ECE), M0
• TNM stage I for HPSCC: T1, N0, M0
Within 2 weeks before randomization, assessment by a Multi-Disciplinary Team (MDT) composed of at least a head and neck/ENT surgeon, medical oncologist, radiologist, radiotherapist, and pathologist of the treatment naïve patient and suitable for either TOS or IMRT based on:
• Contrast enhanced CT and/or MRI done within 4 weeks prior to randomization

• Repeat contrast enhanced CT and/or MRI or US 1 week or less prior to enrollment in case of suspicious nodes <1cm on initial scan if per local practice
• Panendoscopy with assessment of trans-oral exposure for resection.
• peri-nodal infiltration either via CT-scan or MRI.
• ECOG Performance status <= 2;
• Availability of biological material for HPV/p16 testing for OPSCCs
• Age 18 and older; Age 18 to 70 for SGSCC
• Study information and Informed consent discussed by the surgeon and radio-oncologist and signed by the patient.

• Within 2 weeks prior randomization:
• Baseline MDADI score available;
• Adequate bone marrow function as demonstrated by neutrophils count > 1,5 109 /L , platelets count > 75 109 /L, WBC>= 3.0 109 /L;
• Prothrombin time (PT) with an international normalized ratio (INR) <= 1.2
• Partial thromboplastin time (PTT) <= 1.2 times ULN
• Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test no more than 72 hours prior to randomization.
• Patients of childbearing / reproductive potential should agree to use adequate birth control measures for 6 months, especially if they will undergo any radiotherapy treatment at any time during the study. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Exclusion criteria

Any previous anti-cancer therapy for HNSCC (surgery, chemo, radiotherapy or molecularly targeted therapy);
• Any active malignancy (other than non-melanoma skin cancer or localized cervical cancer or localized and presumed cured prostatic cancer) within the last 5 years with ongoing systemic treatment
• Cancer in contact with the internal and/or common carotid artery
• Extension of OPSCC across the midline of the base-of-tongue
• Arytenoid involvement in case of SGSCC
• Infiltration of apex for piriform sinus in case of HPSCC
• Cancer originating from the soft palate or posterior pharyngeal wall
• Requirement of a reconstruction with a free or regional flap (i.e. involvement of >50% of the soft palate)
• Pre-existing dysphagia not related to the oropharyngeal cancer or diagnostic biopsies

• Any psychological, cognitive, familial, sociological or geographical condition potentially hampering compliance with the study protocol, completion of patient reported measures and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Study design

Design

Study phase: 3

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-06-2023
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO

Date:	24-04-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
ClinicalTrials.gov	NCT02984410
CCMO	NL77741.029.21