Thermoradiotherapy for locally Advanced head and Neck Cancer patients - A phase I dose finding study (TANCA-I)

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Primary Objective: To determine the recommended phase II dose (RP2D) of thermoradiotherapy in LA-HNSCC patients. Secondary Objective(s): • Evaluate the Local control, Disease Free Survival and Overall Survival of thermoradiotherapy. • Objective...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON57336

Source
ToetsingOnline

Brief title
Thermoradiotherapy in head and neck cancer

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Laryngeal cancer, Pharyngeal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: financiering door Erasmus MC;Sensius BV en

PPS toeslag (via KWF) ,Sensius BV

Intervention

Keyword: head and neck cancer, phase I trial, radiotherapy, thermotherapy

Outcome measures

Primary outcome

The primary objective of this study is to identify the recommended phase II dose (RP2D) of thermoradiotherapy, according to the specifications given in section 2 and 4 of the study protocol.

The dose limiting toxicity (DLT) trismus will be objectively scored by measuring the mouth opening using a caliper according to a standardized protocol. In short, patients are asked to open their mouth as far as possible and the distance between the incisal edges of the 11 and 41 (or of the dental prosthesis) will be measured. When patients are edentulous and do not wear a dental prosthesis, the alveolar ridge of mandible and/or maxilla will be used (region 11 and 41).

Mouth opening will be measured at baseline, every thermotherapy fraction and regular follow-up time points (end of radiotherapy, 6, 12, 24 weeks post radiotherapy). In addition, the severe DLTs, as mentioned above, will be closely monitored for at the same time points. Therefore, the data collection in the e-CRF should be kept up-to-date at all times. Safety reports will be evaluated every 2 months by the Sponsor and PI during the study.

Secondary outcome

Secondary study parameters/endpoints

• Objective response rate 3 months after thermoradiotherapy, defined as radiological response on CT-scans or MRI with or without histopathological confirmation of residual disease

• Efficacy of TANCA-I in terms of in-field and nodal elective field tumor control upon regular follow-up until 2 years

• Reached target temperatures in selected patients

Other study parameters

For the primary endpoint of this trial, all patients will be monitored until 6 months after the last patient has completed TANCA-I. This will result in a median follow-up of approximately 1 year. This follow-up period will also be sufficient for the analysis of secondary outcomes. Patients will subsequently receive follow-up outside the scope of this trial according to standard of care up to 5 years after treatment. The following parameters are all prospectively collected during routine clinical care follow up and will be evaluated retrospectively:

• Physician-reported grade 3-5 toxicity according to CTCAE v5.0.

• Progression free survival (PFS), 3 years after end of treatment.

• Overall survival (OS), 3 years after end of treatment

• Failures, incidents or performances problems of the HyperCollar3D during treatments.

Study description

Background summary

The prognosis of patients with stage III and IV, so-called locally advanced (LA), head and neck squamous cell carcinoma (HNSCC) is generally poor, with an overall 5-year survival of only 50% [1, 2]. In the Netherlands, the total incidence of head and neck cancer is around 3200 per year (Dutch Cancer Registration). Stage I and II HNSCCs are treated with a single modality consisting of surgery or radiotherapy (RT), while stage III and IV (LA-)HNSCCs are preferably treated with combined modality (surgery, RT, and/or chemotherapy). This is because of the abovementioned low survival rates which are for a large part dependent on the ability to achieve local control of the primary tumor and regional lymph nodes, so the regions with macroscopic tumor [3, 4]. Thermotherapy has the potential to directly target tthe areas at risk for local failure, because of the focussed targeting of all macroscopic tumor sites.

In LA-HNSCC, RT is generally applied using the simultaneous integrated boost (SIB) technique, delivering 54.25Gy of RT dose to regions with high risk to contain microscopic tumor cells and 70Gy of dose to the regions with macroscopic tumor. To enhance the effectivity of the radiotherapy treatment, especially in the macroscopic tumor regions, Cisplatin chemotherapy or the epidermal growth factor receptor (EFGR) inhibitor Cetuximab are generally added to the RT in LA-HNSCC [5, 6]. However, in patients above 70 the addition of systemic therapy to radiotherapy is debatable due to lack of efficacy and increased toxicity. The additional effect of Cisplatin on survival is not observed in patients over 70 years and there is an increase from 6% to 15% in tube feeding dependency after 6 months by Cisplatin chemotherapy[5-7]. Due to the lack of an effective and/or low toxicity sensitizer, the cancer specific survival in elderly patients is worse compared to younger patients with a Hazard ratio of 1.53 (95% CI 1.04-2.25) [8]. Since RT alone is already resulting in significant toxicity in the elderly patients, a new sensitizer with a low toxicity profile is needed for these patients.

Thermotherapy, also called (mild) hyperthermia, is the elevation of tissue temperature to fever-like levels, between 40 and 44 degrees Celsius. Thermotherapy is proven to be effective as radio sensitizer and is reimbursed as part of routine clinical care for cervical carcinoma patients [9, 10]. Preclinical evidence suggests that thermotherapy directly kills cells that are relatively resistant to radio- or chemotherapy. It inhibits the repair of DNA damage caused by radio- or chemotherapy and improves oxygenation in the tumour area, thereby enhancing the effect of RT [11].
In a review of 6 studies using thermotherapy as an adjuvant to RT in HNSCC patients, complete response rate improved from 39,6% to 62,5%, compared to RT

alone [12]. However, these results, although promising, were obtained using so called superficial thermotherapy techniques, only allowing heating up to limited depths [12]. We believe these superficial techniques are less suitable for HNSCC, because tumors and lymph nodes are mostly located deeper into the tissues.

Therefore, at the department of radiotherapy at Erasmus MC, the HyperCollar3D was developed. This is a medical device that -for the first time- allows this so-called deep thermotherapy in the head and neck region, while avoiding sensitive structures [13, 14]. The device is equipped with advanced treatment planning software that enables the physician to mark the tumor area and predict the energy distribution [15].
We have reported on two retrospective cohorts using the HYPERcollar (27 patients) and the next generation device, the HyperCollar3D (22 patients). We used the devices to apply thermotherapy in a compassionate use indication; patients having a recurrent or second primary HNSCC following previous RT in the HN area [16, 17]. In the latter cohort, using the Hypercollar3D, we observed an unexpected incidence of acute trismus (limited mouth opening) maximal grade II in 4 out 22 patients[17]. Notably, following the first 3 cases of trismus in the first 5 patients, the dose rate to the tumor region was lowered, after which in only 1/17 patients a trismus was observed, suggesting a dose-effect relationship. Whether occurrence of trismus or other toxicity was related to the thermotherapy is not known. Since thermotherapy dosage in the past was empirical and analysis was performed post-hoc, dose effect relations could be not determined reliably. In addition, it is also unclear whether the applied dose in these recurrent HNSCC patients, would be the optimal dose in previously untreated, primary HNSCC patients.

We are now moving away from a *last resort/compassionate use* treatment in the re-irradiation setting towards the first line treatment of primary HNSCC patients and therefore we propose to perform a dose finding phase I trial. The reasons for a dose finding study are 1.) to obtain more evidence of the safety of thermoradiotherapy in the HN region and 2.) to find the highest dose that is tolerable and does not lead to unacceptable acute and/or late side effects. The latter is highly important given the temperature-effect relation of thermotherapy, as clearly observed in other tumor sites [10, 18].

Until today, it has not been possible to predict the temperatures in the heated area due to unknown tumor and normal tissue blood perfusion, which varies between patients and tumors. Invasive measurement of temperatures in head and neck tumors is notably difficult, due to inability to reach the primary tumor in the pharynx or larynx and complication risks like bleeding and infection. Therefore dosage of thermotherapy in this study will not be based on measured or modelled temperatures, but instead on the delivered energy, with a physical unit expressed by Joule/kilogram.

The dose levels in our study were selected based on previous data from our

center and others. We took into consideration the dose to achieve a therapeutic rise in temperature in the target as well as the dose at which toxicity was observed in the normal tissues([19, 20] and unpublished data Erasmus MC). As the primary endpoint of this trial is the MTD consisting of feasibility and DLT, we decided to base our dose escalation on the maximal dose to the normal tissues. Since we previously observed that the maximal dose to the normal tissues is linearly correlated to dose to the target (unpublished data from Erasmus MC), we also escalate the dose to the target in a linear manner, in this way.

In thermotherapy a target temperature of at least 40 degrees Celsius is considered therapeutic. Although the dose escalation is based on energy applied in this study, we do aim to determine the target temperature whenever possible. Using ultrasound guidance, it is safe to insert a temperature probe in the neck close to a pathologically enlarged lymph node (=target). To determine if therapeutic temperatures are reached during the dose escalation, we would like to obtain an invasive thermometry measurement in one (out of the seven) thermotherapy fractions. To this end, a separate informed consent will be asked to patients to insert a neck catheter and measure target temperature in one thermotherapy fraction. We have chosen for a separate informed consent for this, because we do not want to hamper inclusion of the primary endpoint of the trial. In addition, a few patients willing to obtain invasive temperature measurements would suffice to reach our goal of determining obtained target temperatures in the dose escalation process.

The primary endpoint of the phase I dose escalation trial will be the recommended phase II dose (RP2D) of thermoradiotherapy in primary HNSCC patients. This RP2D is tolerable and does not lead to increased acute and late effects of the radiotherapy. This trial will be conduc

Study objective

Primary Objective:
To determine the recommended phase II dose (RP2D) of thermoradiotherapy in LA-HNSCC patients.

Secondary Objective(s):

• Evaluate the Local control, Disease Free Survival and Overall Survival of thermoradiotherapy.

• Objective response rate will be evaluated by radiological response on CT-scans or MRI at 3 months post treatment, with or without histopathological confirmation of residual disease. These variables will be categorical, data will be descriptive in nature. The best response will be reported.

• Evaluate the doctor and patient reported outcome measures on acute and late

toxicity after thermoradiotherapy.

• Measure reached target temperatures (in selected patients)

• Evaluate the safety and performance of the HyperCollar3D.

Study design

The safety of addition of thermotherapy to radiotherapy will be evaluated in a phase I dose finding study. The thermotherapy dose will be increased per group of patients and the tolerability and toxicity will be closely monitored. The thermotherapy dose levels are described in section 4. The primary endpoint of this trial is the recommended (phase II) dose (RP2D) of thermotherapy added to radiotherapy.

The RP2D is defined as the dose level below the dose level for which any of these events occur:
1. the incidence of dose limiting toxicity (DLT) Trismus is not higher than baseline
2. any occurrence of severe DLT
3. the infeasibility to apply the dose level is more than 33%
(Feasibility/tolerability rules are described in section 4).

Rationale of DLT definition
In previous cohorts, we observed no increased late toxicity other than trismus (limited mouth opening) maximal grade II following thermoradiotherapy in 4/22 patients. Therefore, trismus is a potential toxicity to occur that could be dose limiting. A recent study by the group of prof. Dijkstra (UMCG) reported on the incidence of trismus at 6 months post treatment in HNSSC patients treated with radiotherapy [21]. Trismus was defined as a mouth opening of <=35 mm, which included potentially all CTCAE gradings, but mostly grade I trismus (personal communication dr. Dijkstra). The incidence of new trismus in patient having no trismus before treatment, was 28% until 6 months post-treatment [22].

Therefore, the RP2D is considered the dose for which the incidence of the DLT trismus (defined by a mouth opening of <=35 mm) until 6 months is at most 28%. The incidence of trismus as defined above is monitored using the TITE-BOIN design described below.

Dose-escalation design and DLT trismus
A TITE-BOIN design will be used to guide dose escalations regarding the DLT *trismus* as defined by a mouth opening of <=35 mm until 6 months. A Uniform non-informative Prior for the occurrence of DLT was used, (i.e., a priori the current dose is equally likely to be below, equal to, or above the RP2D.The target toxicity probability, i.e., the toxicity probability of the RP2D, was specified to be 28%. A cutoff probability to eliminate an overly toxic dose for safety of 0.95 was specified. This means that a dose will be eliminated if

the posterior probability that the current dose is above the RP2D is more than 95% (this value is the general recommendation in BOIN designs). There are 5 dose levels defined (see paragraph 4).

The first cohort of three patients will be treated at dose level 2 and after that cohorts of six patients will be treated.

Operating characteristics
The operating characteristics of the design after the first 6 patients were explored by simulation using the BOIN software developed by at the MD Anderson Cancer center, version 1.1.0. Six scenarios were explored, each belonging to a different true RP2D. The simulation was started at dose level 3, and it was assumed that 24 more patients would be treated, that accrual would follow a Poisson process with a rate parameter of 1 patient per month. The operating characteristics show that the design selects the true RP2D, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.28 (table 3 below).

In addition to trismus as objectified by a mouth opening of <=35 mm until 6 months, we define the following toxicities until 6 months as severe DLT:
• Grade III trismus
• Grade IV mucositis
• Grade IV dermatitis
• Grade III or IV osteo- or soft tissue necrosis
• Grade IV burn wound
• Grade IV tumor hemorrhage
• Grade IV laryngeal edema

These severe DLTs are not expected to occur at all:
Therefore, as soon as a single severe DLT (as defined above) is observed, the dose level will immediately be closed for inclusion of new patients, irrespective of any escalation rule from the TiTE-BOIN design. Those rules are only used for trismus as ordinary DLT (i.e., mouth opening of <=35 mm, but not trismus grade III (trismus resulting in inability to adequately hydrate or aliment orally).

In this single center study, the local data manager and local investigator will ensure to keep the study database (e-CRF) up to date, ensuring all patients enrolled for a certain dose level (maximal 11/12) are update on DLT at the time of inclusion of a new patient.

Intervention

General description of investigation treatment

Treatment preparation:

The preparations for the thermotherapy treatment will be performed in the radiotherapy department. First, an individualized head cushion and nose bridge fixation are made to be able to fixate the head but leaving as much space as possible for cooling of the head. Also, an individualized dental mould will be made, to fix the oral temperature probe to the mucosa of the cheek. Next, patients will receive an CT scan in this fixed position. Next, the patient is positioned in the HyperCollar3D to check and record the optimal positioning in the device. The latter is necessary for optimal treatment planning. The mouldings, CT scans and preparation at the device are all performed on the same day but require one additional hospital visit for the patient.

Before each thermotherapy treatment, a thermometry probe will be placed intra-orally using the dental mould and thermometers will be placed on the skin of the neck and the cheeks. Patient will be positioned in the HyperCollar3D applicator (Figure 1 in the study protocol) and the water bolus will be filled around the neck and cheeks.

During each thermotherapy treatment, the patient will be instructed to mention any unpleasant sensation, such as a burning, pressure, or pain. By switching off the power briefly (30 sec), it will be established if the pain was caused by the radiated power. If this is the case, the treatment settings (phase and amplitude) and/or applied power will be adjusted. In case of skin complaints, water cooling bags can be applied. The treatment includes a warm-up time of approximately 15 minutes in which the energy is slowly increased to the maximal dose rate. This is followed by a steady state phase of 60 minutes, in which the energy deposition is kept at a more constant level.
Thermotherapy is applied weekly following the radiotherapy fraction, within approximately 2 hours.

If during treatment the anatomy of the patient changes significantly due to tumor regression or weight loss, the initial plan may not be suitable anymore. In this case an new planning-CT will be made for replanning of the thermotherapy. This will NOT require an additional visit to the hospital, as the new CT will be made before or after a radiotherapy fraction.

Upon additional informed consent for invasive thermometry (see paragraph 9.6), at one or two of the thermotherapy sessions, a catheter will be placed inside or close to a pathological neck lymph node by a head and neck surgeon or intervention radiologist under local anaesthesia. This catheter will be used for invasive thermometry during one or two thermotherapy fractions and will be removed directly afterwards. Therefore, the catheter will only be in place while the patient is in the hospital.

Dose escalation and feasibility rules
The primary target of the thermotherapy treatment is the gross tumor volume of the primary tumor and any pathological lymph nodes, named the *target* from now onwards. Thermotherapy dose is expressed as the Specific Absorption Rate (SAR),

quantifying the delivered electromagnetic energy to the target and healthy tissues. To optimize the SAR to the target and minimize the SAR to healthy tissues, in-silico treatment planning is performed based on the acquired CT scan in the treatment position. From this thermotherapy treatment plan, the maximal SAR to the target and the maximum SAR to healthy tissues (also called SAR hotspot) are important parameters. From previous clinical thermotherapy plans it was shown that the relation between SAR to target and SAR hotspot are strongly associated and is linear. The tolerability and likely toxicity are more related to SAR to healthy tissues compared to SAR to the target. We therefore choose the SAR hotspot to be the dose parameter to dose escalate our thermotherapy treatments on.

The intended dose levels are:
1. SAR to normal tissue in the treatment plan= 40 W/kg
2. SAR to normal tissue in the treatment plan= 75 W/kg
3. SAR to normal tissue in the treatment plan= 100 W/kg
4. SAR to normal tissue in the treatment plan= 125 W/kg
5. SAR to normal tissue in the treatment plan= 150 W/kg

Tolerability of the investigational treatment
In case of pain or discomfort during the thermotherapy treatment, optimization of the thermotherapy treatment plan will take place in real-time/online, resulting in replacement of the maximal SAR to another place within the normal tissues. To maintain the SAR to normal tissue, optimization is only allowed if the delivered energy to normal tissues as a whole is maintained. If maintenance of the delivered energy to normal tissues is not possible, a maximum decrease of 20 percent is allowed, for no more than 10 out of 60 minutes during the steady state heating.
When more than 20 percent power decrease is needed and/or when 10 minutes with less power (until 20 percent) are exceeded, the fraction is considered not feasible to apply.
If 2 or more out of 4 thermotherapy fractions in the HYDRA fractionation scheme (20 fractions = 4 weeks) or 3 or more out of 7 thermotherapy fractions in the normofraction scheme (35 fractions = 7 weeks) are not applied due to infeasibility as defined above, that dose level is considered not feasible for that individual patient.
Thermotherapy fractions that were not applied due to logistical and/or social reasons and/or medical reasons not related to the study treatment are excluded for these rules.
If it is not feasible to apply the intended dose in >33% patients per dose level group (for example 2 out of 3 patients or 3 out of 6 patients or 5 out of 12 patients), the intended dose level is considered intolerable and elimated (see paragraph 2).
Of note, patients for which the dose level is considered infeasible to apply are offered to finish any remaining thermotherapy fractions with the previous dose level that was feasible and did not show DLT. These patients will not be

evaluated for DLT (paragraph 7.5).

Study burden and risks

Patients with a locally advanced (LA)-HNSCC are at high risk for locoregional recurrence following primary radiotherapy and therefore have an indication for radio-sensitisation, mostly done by using Cisplatin. Due to age and co-morbidity, Cisplatin cannot be applied in all patients. We select these sensitizer *unfit* patients for our study because of 1.) the need for treatment intensification, while 2.) no effective radio sensitizer is available.
Potential known acute side effects of thermotherapy in other disease sites are increased fatigue, local pain, and a small chance of a self-limiting burn wound. In salvage/re-irradiation HNSCC patients, we previously applied thermotherapy in a compassionate use setting. We observed no acute or late toxicities that could potentially be attributed to the thermotherapy, except for acute grade I-II trismus in 4/22 patients. Going to first line treatment, we believe a dose finding study is therefore warranted for two reasons: 1.) to proof the safety of thermoradiotherapy in the head and neck region and 2.) finding the highest dose that is tolerable and does not lead to increased acute and late toxicity compared to radiotherapy alone.
The latter is important, as a clear dose/temperature-effect relationship has been reported for thermotherapy in other tumor sites. Ensuring clinical safety and knowing the maximal tolerable dose of thermotherapy are both pivotal factors, considering a potential future phase II trial -not in this protocol- to further explore the effectivity of thermoradiotherapy in HNSSC patients.

In summary, we will perform a phase I dose finding study of thermoradiotherapy in HNSCC patients amenable to first line radiotherapy treatment. Patients undergoing thermoradiotherapy in this study could have a potential benefit, as they might experience a higher chance of tumor control compared to radiotherapy alone.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40

Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age >= 18 years

• WHO 0-1

• Mouth opening of >= 40 mm for woman and >= 45mm for man before treatment

• Squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx proven by cytology / histology.

• Locally-advanced disease (stage III-IV).

• Curative intend treatment with radiotherapy in the primary setting with a contraindication for systemic adjuvant treatment.

• Ability to understand the requirements of the study and to give written informed consent, as determined by the treating physician.

• Written informed consent.

Exclusion criteria

• Patients previously treated by radiation on the same target volume.

• Any condition or circumstance potentially hampering compliance with the

follow-up schedule.

• Patients having pacemakers or clustered metal markers (with a total length >2 cm of metal markers in direct contact).

• Tumor location caudal to a tracheostomy (this prevents penetration of the microwaves to the tumor).

• Anatomical boundaries of the shoulders prohibiting positioning of the applicator.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2025
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Generic name:	HyperCollar3D
Registration:	No

Ethics review

Approved WMO

Date:	12-03-2025
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NCT06761937
CCMO	NL84322.078.24