



Individual elective lymph node irradiation for the reduction of complications in head and neck cancer patients (iNode): A phase-I feasibility trial protocol

Floris C.J. Reinders^{*}, Mischa de Ridder, Patricia A.H. Doornaert, Cornelis P.J. Raaijmakers, Marielle E.P. Philipens

Department of Radiotherapy, University Medical Centre Utrecht, Utrecht, the Netherlands

ARTICLE INFO

Keywords:

Magnetic resonance imaging
Lymph nodes
Radiotherapy
Squamous cell carcinoma of head and neck
Head and neck neoplasms
Elective neck irradiation

ABSTRACT

Introduction: The long-term complication rate in head-and-neck squamous cell carcinoma (HNSCC) patients caused by radiotherapy (RT) can be decreased by restricting elective neck irradiation (ENI) from large adjacent lymph node levels to only individual elective lymph nodes. The primary objective of this study is to treat the first HNSCC patients with individual elective lymph node irradiation by means of a Magnetic Resonance-linac (MR-linac) in order to assess the feasibility.

Methods and analysis: In this phase I feasibility study, 20 patients will be included with histologically proven cT2-4N0-1M0 HNSCC originating from the oropharynx, hypopharynx or larynx, planned for treatment with primary radiotherapy and bilateral elective neck irradiation (ENI). Patients will be treated with 35 fractions in six weeks, according to the DAHANCA schedule. Individual lymph nodes inside the conventional lymph node levels will be categorized in low-risk, intermediate-risk and high-risk based on cytology, histology and imaging parameters. Low-risk and intermediate-risk lymph nodes will irradiated in 20 and 23 fractions respectively, with a fraction dose of 2 Gy (=40/46 Gy EQD2). The high-risk lymph nodes and the primary tumor will be irradiated in 35 fractions of 2 Gy (=70 Gy equivalent dose in 2 Gy fractions (EQD2)). To limit treatment burden, 20 fractions will be applied on the MR-linac. The last 15 fractions (sequential boost at the primary tumor, intermediate-risk and high-risk lymph nodes) will be applied on a conventional linear accelerator. The main study endpoint is the percentage of fractions that are successfully completed on the MR-linac.

Ethics and dissemination: With individual elective lymph node irradiation we expect less toxicity and a better quality of life for HNSCC patients. However, as the treatment time on the MR-linac will be longer (30–45 vs 15 min per fraction) we need to examine if patients can endure this new treatment concept.

1. Introduction

Every year approximately 3000 patients are diagnosed with head and neck squamous cell carcinoma (HNSCC) in the Netherlands. The majority of patients is treated with radiotherapy. Approximately 50% of these patients develop late toxicity after treatment with radiotherapy (RT) such as dysphagia [1], xerostomia [2], hypothyroidism [3] and carotid stenosis [4,5]. The quality of life of HNSCC patients is negatively influenced by this late toxicity [6,7]. Most HNSCC patients treated with RT receive elective neck irradiation (ENI) to unilateral or bilateral lymph node levels for the treatment of possible, non-visible regional metastases (i.e. occult metastasis). The introduction of ENI in the 1960's

decreased regional recurrences (RR) rates from approximately 20% to 2.5% [8]. However, despite advances in cancer imaging, the concept of ENI remained largely unchanged [9]. With recently reported regional recurrences (RR) rates of only 1–5% [10,11], it might be possible to decrease the radiation dose used with ENI.

Several studies decreased the dose to the elective neck in order to reduce late toxicity rate for HNSCC patients. Table 1 provides an overview of finished and ongoing studies regarding dose de-escalation of ENI. In two studies the dose to the elective neck was successfully decreased to 36–40 Gy [12,13]. Other studies excluded lymph node levels based on imaging parameters [14] or lymph node drainage patterns [15], also without increasing the RR rate. In one ongoing study the

^{*} Corresponding author.

E-mail address: f.c.j.reinders-2@umcutrecht.nl (F.C.J. Reinders).

<https://doi.org/10.1016/j.ctro.2022.100574>

Received 19 December 2022; Accepted 29 December 2022

Available online 30 December 2022

2405-6308/© 2022 The Author(s). Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1
Ongoing and finished studies regarding alternative treatment to the elective neck volumes.

Author name, year, study type, trial number, reference	Number of patients ((C)ontrol / (I)ntervention / (NA) Not Applicable)	Target area definition inside the lymph node levels	Total dose in Gy (fractions*fraction dose)	Concurrent chemotherapy (%)	Median follow-up ((Y)ear/(M)onth)	Regional recur. % (p-value if applicable)
Ongoing studies						
van den Bosch et al., 2017, prospective RCT, trial number: NCT02442375, [16]	100 (C)	I. Lymph nodes in which positive cytology or necrosis or short-axis diameter ≥ 10 mm	I. 62 (33*1.88)	No	–	–
	200 (I)	II. Elective lymph node regions I. Lymph nodes in which cytology or necrosis or high FDG-uptake (SUR ≥ 2.0) II. LNs with summed long- and short-axis ≥ 17 mm + intermediate FDG-uptake (SUR ≥ 1.5 - < 2.0) III. Elective lymph node regions	II. 48 (33*1.45) I. 62 (33*1.88) II. 58 (33*1.76) III. 42 (33*1.27)	No	–	–
de Veij Mestdagh et al., 2019, prospective cohort, trial number: NCT03968679, [17]	90 (NA)	I. Lymph nodes with macroscopic tumor II. Unilateral elective neck region (if drainage is unilateral or if drainage is bilateral but contralateral sentinel node is negative)	I. 70 (35*2.00) II. 54.25 (35*1.55)	Allowed	–	–
Finished studies						
Sher et al., 2021, prospective phase II, [14]	72 (NA)	I. Lymph nodes with macroscopic tumor II. Elective LN levels (level III-IV only if adjacent proximal level contains pathologic lymphadenopathy)	I. 64 (20*2.00 + 15*1.60) II. 40 (20*2.00)	Allowed (78 %)	2 (Y)	10.0 %
de Veij Mestdagh et al., 2020, prospective cohort, [22]	50 (C)	I. Lymph nodes with macroscopic tumor II. Bilateral elective lymph node regions	I. 70 (35*2.00) II. 54.25 (35*1.55)	Allowed (20 %)	33 (M)	4.0 %
	50 (I)	I. Lymph nodes with macroscopic tumor II. Unilateral elective lymph node region (if drainage is unilateral)	I. 70 (35*2.00) II. 54.25 (35*1.55)	Allowed (20 %)	33 (M)	Not reported
Deschuymer et al, 2020, prospective RCT, [12]	96 (C)	I. Lymph nodes with macroscopic tumor II. Elective lymph node regions	I. 70 (EQD2) II. 49.6–56 (32*1.75 / 30*1.85 / 30*1.7 / 25*2)	Allowed (65 %)	7.6 (Y)	7.5 % (ref)
	95 (I)	I. Lymph nodes with macroscopic tumor II. Elective lymph node regions	I. 70 (EQD2) II. 40–48.69 (32*1.53 / 30*1.40 / 30*1.60 / 20*2)	Allowed (69 %)	7.6 (Y)	14.0 % (0.10)
Maguire et al., 2018, prospective phase II, [13]	54 (NA)	I. Lymph nodes with macroscopic tumor II. Elective lymph node regions	I. 70 (35*2.00) II. 36 (35*2.00)	Yes (100 %)	36 (M)	0 %

de-escalation of ENI is based on positron emission tomography uptake [16], while another ongoing study further investigates the selection of lymph node levels based on drainage patterns including a sentinel node procedure [17]. Considering all studies performed on this subject, it is thought that lowering the dose in the elective neck to 35–40 Gy EQD2 (Equivalent dose at 2 Gy fractions) does not result in an increased RR rate.

Still all finished and ongoing studies use conventional lymph node levels as target volumes, which are contoured on anatomical boundaries using Computed Tomography (CT) [18]. These lymph node levels have a large volume and consequently their irradiation causes side effects to nearby organs at risk (OARs). With modern Magnetic Resonance Imaging (MRI) techniques, it is possible to visualize the individual elective lymph nodes inside the lymph node levels. The term elective means that there is no suspicion of macroscopic tumor load based on radiology or histology, but occult metastases might occur in these lymph nodes. We expect that occult metastasis will occur inside lymph nodes and not in the fatty tissue surrounding the lymph nodes (i.e. the entire lymph node levels). Converting conventional ENI into specific dose delivery to only elective lymph nodes will reduce radiation dose to healthy tissues and possibly reduce the late toxicity rate for patients with HNSCC without compromising regional control.

Our new concept is called individual elective lymph node irradiation in which target volumes of the lymph node levels are reduced to only individual elective lymph nodes. The primary tumor and pathological lymph nodes will receive the conventional dose of 70 Gy. Individual elective lymph node irradiation will be explored on the recently developed MR-linac. The MR-linac is a linear accelerator combined with an MRI-scanner and facilitates the integration of MRI in the radiotherapy planning and treatment. With the MR-linac it is possible to identify (small) individual elective lymph nodes and treat them accordingly while the patient is on the treatment table [19,20]. This in contrast to conventional linear accelerator machines on which small individual elective lymph nodes are not visible with cone beam CT (CBCT). In our previous treatment planning study [21], individual elective lymph node irradiation showed favorable results compared to conventional treatment in terms of OAR sparing. With our new treatment concept we observed mean dose reductions of >5 Gy in carotid arteries, thyroid and submandibular glands.

The primary objective of this study is to treat the first HNSCC patients with individual elective lymph node irradiation on the MR-linac and assess its feasibility. We consider individual elective lymph node irradiation feasible if on average at least 85% of all fractions could be performed on the MR-linac. The secondary objectives are to monitor patient safety, toxicity and tolerability of this new treatment concept.

2. Methods and analysis

2.1. Study design, inclusion and exclusion criteria

This is a monocenter phase I feasibility study, that will be performed at the UMC-Utrecht. Twenty patients with T2-4N0-1M0 HNSCC originating from the larynx, oropharynx or hypopharynx will be treated according to our new treatment design for the elective neck volumes. The inclusion and exclusion criteria are listed in Table 2.

2.2. Treatment description

2.2.1. Imaging and fixation procedures

For all HNSCC patients undergoing RT treatment, a thermoplastic fixation mask is made. Subsequently, patients will undergo a treatment-planning Computed Tomography (CT) and MRI in this mask. The CT is acquired with a slice thickness of 3 mm and a minimal in-plane resolution of 1 mm². In the future, a synthetic CT scan will be reconstructed from the MR-images to support an MR-only workflow. The MRI protocol for HNSCC patients consists of different sequences. Of these sequences the water-only image of the multiple Dixon T2-weighted turbo spin echo (T2 mDixon TSE) scan [23] will be used for identification of individual lymph nodes (TE: 100 ms, TR: 3000 ms, flip angle: 90°, slice thickness: 3 mm, in plane reconstructed resolution: 0.86 mm²).

2.2.2. Delineation of target areas

According to conventional treatment, target areas and OARs will be delineated on the planning-CT based on international guidelines [18,24]. The MRI scan will be matched to the planning-CT and provides additional anatomical information regarding the primary tumor, individual lymph nodes and OARs. Lymph nodes are identified as structures with a hyperintense signal inside the conventional nodal neck volumes (II-IV) in at least two transverse slices. Lymph nodes in level Ia/b, V, VIa/b or VIIa are added to the target volumes only if these levels are indicated according to the conventional clinical guidelines.

A trained neural network previously developed in our center will supply a proposition of delineations of the lymph nodes and elective neck volumes (levels I-V). All proposed delineations will be reviewed by the radiation oncologist and adapted if necessary.

(Elective) lymph nodes will be divided in high-risk, intermediate-risk and low-risk:

- High-risk lymph nodes (also known as suspicious, pathological or positive lymph nodes during conventional treatment) compromises all lymph nodes with positive cytology or with necrosis on imaging.

Table 2
Inclusion and exclusion criteria to participate in the inode trial.

Inclusion criteria	Exclusion criteria	
Squamous cell carcinoma of the larynx, oropharynx or hypopharynx	Concurrent chemotherapy or cetuximab	Age < 18 years
T2 –T4 stage	Patients unsuited for MRI imaging	WHO performance status ≥ 2
Indication for curative primary (accelerated) RT	Synchronous malignant tumor(s) at another site	Distant metastasis
Indication for bilateral ENI	Previous malignancies in the HN region treated with surgery, chemotherapy or radiotherapy, except for tumors treated with endoscopic glottic laser microsurgery	Mental or physical impairment causing the participant to be unable to fill out questionnaires
N0-1, based on bilateral ultrasound / MRI / PET of the neck	A history of malignant disease for which treatment was ended < 2 year before diagnosis of the HNSCC, except basal cell carcinoma Previous dissection of lymph nodes in the neck	Participation into another interventional study

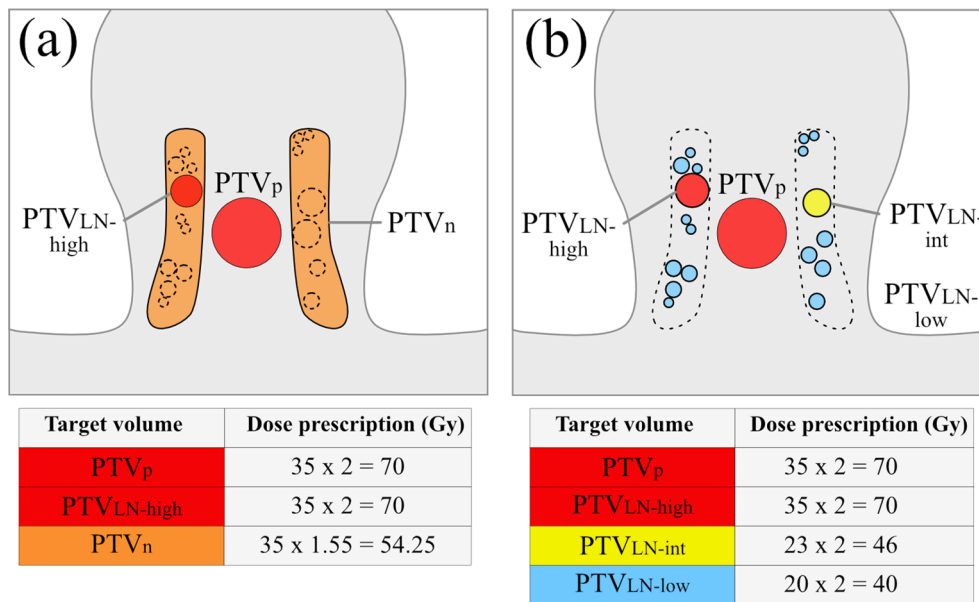


Fig. 1. (a) Conventional dose description of hypopharyngeal, oropharyngeal or laryngeal cancer with an indication for bilateral elective neck irradiation and (b) the new strategy to irradiate individual (elective) lymph nodes. PTV_p = planning target volume of the primary tumor, PTV_n = planning target volume of the conventional elective neck volumes, PTV_{LN-high / int / low} = Planning target volume of high-risk, intermediate-risk and low-risk lymph nodes.

If a PET-CT scan is available and shows pathological lymph nodes, these nodes are also considered high-risk.

- Intermediate-risk lymph nodes comprise all lymph nodes with a summed long- and short-axis diameter ≥ 17 mm in the transverse plane without positive cytology or necrosis according to the criteria of the UPGRADE study [16].
- Low-risk lymph nodes comprise all other visible lymph nodes in which the major axis in the transverse plane is 4 mm or larger.

2.2.3. Radiation dose

The low and intermediate-risk lymph nodes will be irradiated with a dose of $20 \times 2 \text{ Gy} = 40 \text{ Gy}$ and $23 \times 2 \text{ Gy} = 46 \text{ Gy}$ respectively (Fig. 1). The high-risk lymph nodes and the primary tumor will receive a conventional dose of $35 \times 2 \text{ Gy} = 70 \text{ Gy}$.

2.2.4. Fractionation schedule

Patients will be treated according to the widely used DAHANCA schedule [25]. The DAHANCA schedule consists of 35 fractions applied in six weeks. In the first week, patients receive five fractions on Monday up until Friday. From week two to six, patients also receive a second fraction on Friday with a minimum time interval of six hours (Fig. 2).

In the first 20 fractions, the primary tumor and all low-risk / intermediate-risk / high-risk lymph nodes will be irradiated once a day in the first four weeks on Monday to Friday (mornings). As (small) low-risk lymph nodes will not be visible on the conventional cone beam CT, these fractions will be applied on the MR-linac using the Intensity

Modulated Radiation Therapy (IMRT) technique with 17 beams.

After 4 weeks of radiation treatment, tumor visualization is not clear anymore on MRI due its therapeutic effects [26]. Therefore, and because in the remaining fractions only the intermediate and high doses volumes are targeted, the other 15 fractions will be applied on a conventional linear accelerator (linac) with Volumetric Modulated Arc Therapy (VMAT). The fractions on the conventional linac are shorter and will therefore also reduce treatment burden for the patient. Three of the 15 fractions will be directed to intermediate-risk / high-risk lymph nodes and the primary tumor. This will take place in week 2, 3 and 4 on Friday afternoons. The other twelve fractions are administered in week 5 and 6, directed to the high-risk lymph nodes and the primary tumor.

In total, 3 different plans will be made: one MR-linac plan for the low-risk / intermediate-risk / high risk lymph nodes and the primary tumor (20 fractions), one conventional VMAT plan for the intermediate-risk / high-risk lymph nodes and the primary tumor (3 fractions) and one conventional VMAT plan for only the high-risk lymph nodes and the primary tumor (12 fractions) (Fig. 2). At the beginning of the fourth week, a new planning-CT will be made in the same fixation mask. Together with the last online MRI on the MR-linac, target areas and OARs will be re-contoured to make the conventional VMAT plan for week 5 and 6.

2.2.5. Position verification and planning target volume (PTV) margins

For the high-risk lymph nodes and the primary tumor, conventional margins for patients with HNSCC cancer are used in this study. In order

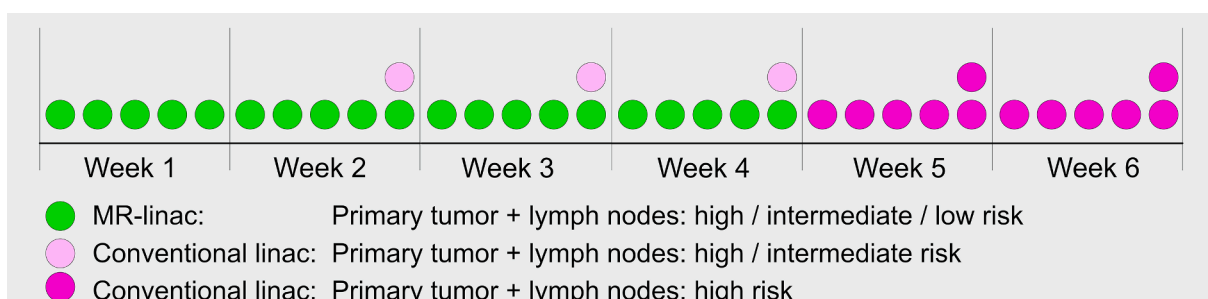


Fig. 2. Fractionation schedule for patients participating in the iNode trial.

Table 3

Target volumes, CTV margins, PTV margins and dose prescriptions for the iNode trial. GTV = Gross tumor volume, CTV = Clinical Target Volume, PTV = Planning Target Volume.

Target volumes	Delineations and CTV and PTV margins		Dose prescription to PTV
1. Primary tumor	GTV _p	Includes all visible tumor identified and delineated on CT/MRI	20 * 2 Gy (MR-linac) +15 * 2 Gy (VMAT)= 70 Gy
	CTV _p	<i>Oropharynx</i> : GTV _p + 5-mm (70 Gy) and + 10-mm (40 Gy) margin in all directions (excluding air and bony tissue)	
	PTV _p	<i>Larynx/hypopharynx</i> : GTV _p + 6-mm margin in all directions (excluding air and bony tissue) <i>Oropharynx</i> : CTV _p + 3/4/5-mm margin in all directions (depending on subsite and mobility) <i>Larynx/hypopharynx</i> : CTV _p + 3, 4 and 6 mm in respectively lateral, ventro-dorsal and cranio-caudal directions. When on the pretreatment cine-MRI the GTV moves outside the CTV in cranial-caudal direction, an 8-mm margin is applied in cranial-caudal direction.	
2. High-risk lymph nodes (LN-high)	GTV _{LN-high}	High-risk individual lymph nodes, defined as lymph nodes with positive cytology, histology or with necrosis on imaging	20 * 2 Gy (MR-linac) +15 * 2 Gy (VMAT)= 70 Gy
	CTV _{LN-high}	GTV _{LN-high} + 5 mm margin in all directions (excluding air and bony tissue)	
	PTV _{LN-high}	CTV _{LN-high} + 3 mm	
3. Intermediate-risk lymph nodes (LN-int)	CTV _{LN-int}	Intermediate-risk lymph nodes, defined as lymph nodes with a summed long- and short-axis diameter ≥ 17 mm without positive cytology or necrosis	20 * 2 Gy (MR-linac) +3 * 2 Gy (VMAT)= 46 Gy
	PTV _{LN-int}	CTV _{LN-int} + 5 mm	
4. Low-risk lymph nodes (LN-low)	CTV _{LN-low}	Low-risk lymph nodes, defined as lymph nodes inside the conventional elective neck volumes identified and delineated on MRI in at least 2 transverse slices in which the major axis in the transverse plane is 4 mm or larger	20* 2 Gy (MR-linac)= 40 Gy
	PTV _{LN-low}	CTV _{LN-low} + 5 mm	

to guarantee a highly accurate irradiation of a multitude of target areas over the complete length of the neck, a retrospective imaging study was performed regarding the visibility and displacement patterns of elective lymph nodes during RT [20]. Based on this study and additional analysis of lymph node dose coverage, we will use a PTV margin of 5 mm around low-risk and intermediate-risk lymph nodes. The target volumes, CTV margins, PTV margins and dose prescriptions can be found in Table 3.

2.2.6. Treatment adaptation on the MR-linac

The MR-linac provides the possibility to adapt the radiation treatment while the patient is on the treatment table. Two workflows of treatment adaptation are available on the MR-linac:

1. The first workflow is called 'adapt to position' (ATP) workflow. ATP allows for plan adaptation based on the online patient position as seen on the MRI-scan performed on the MR-linac. As the delineations on the radiotherapy plan are not adapted but shifted, this procedure can be seen as a conventional position verification procedure. Duration of one fraction with ATP for HNSCC patients will be 15–30 min.
2. The second workflow is called 'adapt to shape' (ATS) workflow. With ATS, all contours of target volumes and OARs will be adapted based on the new patient anatomy as seen on MRI acquired on the MR-linac. A new RT plan is created while the patient is on the treatment table. Duration of one fraction with ATS for HNSCC patients will be 45–60 min.

Since the radiotherapy treatment of HNSCC includes multiple targets and complex dose distribution, the ATS workflow is momentarily too time consuming for all 35 fractions. Furthermore, the changes in head-and-neck anatomy are gradual during the long treatment course and do not require this full plan adaptation every day. Consequently, patients in the iNode study will be treated on the MR-linac with ATP every-five fractions alternated by (an offline) ATS for one fraction at the beginning of each week.

Before every fraction performed with ATP, it will be checked whether all target delineations still align with the consisting radiotherapy plan. If the target delineations are considered not adequate, a change to ATS workflow will be made. The criteria to switch from ATP to

ATS are in line with the conventional guidelines in our department: 1. The current CTV of the target volumes extends outside the defined PTV and 2. The body contour variation is larger than 1 cm. In addition to conventional guidelines, new lymph nodes appearing on MRI during treatment (in at least two transverse slices with a minimum transverse diameter of 4 mm) will also require changing from ATP to ATS.

To reduce treatment burden, the ATS workflow will be performed offline. Offline ATS means the treatment plan will be adapted and optimized for target volume and OAR changes after the patient has left the treatment table. The new treatment plan will be applied starting from the next fraction. With offline ATS, the total procedure on the MR-linac will take the same time as the ATP workflow.

2.2.7. Follow-up procedures

Patients will be included in the regular follow-up program. Additionally, an ultrasound of both sides of the neck will be performed by a radiologist at 8, 12 and 18 months. A fine needle biopsy will be performed in case of a suspicious node. Furthermore, patients will also undergo hearing tests before and after RT treatment to investigate the occurrence of hearing impairment due to the noise inside the MR-linac.

2.3. Endpoints

2.3.1. Main study endpoint

The percentage of fractions performed on the MR-linac according to the new treatment concept. We consider individual elective lymph node irradiation feasible if on average more than 16 out of 20 fractions can be performed on the MR-linac (based on a per-protocol analysis). Either inadequate patient tolerability, contouring/planning issues or machine down time could lead to missing fractions.

2.3.2. Secondary study endpoints

Regarding patient safety.

- Regional recurrence occurring inside the elective neck volumes at 2 years follow-up.

- Difference in hearing function measured by audiometry to assess MR-related hearing changes between baseline and one week after RT treatment.

Regarding RT toxicity.

- Patient reported outcomes (PROs) will be measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 /HN35). Patients will be invited to fill out questionnaires at baseline and 3, 6, 12 and 24 months after treatment.
- Common Terminology Criteria for Adverse Events (CTCAE) will be filled in by the radiation oncologist at baseline and 3, 6, 12 and 24 months after treatment.

Regarding patient tolerability.

- Patient reported experience measurements (PREMs) regarding tolerability of treatment on the MR-linac will be obtained with the previously validated questionnaire of the PERCEIVE study (METC-protocol number: 20–624/C). Patients will be asked to fill out PREMs at three time points: after the first, the 10th and the last fraction.

2.3.3. Other study parameters

- Patient and tumor characteristics.
- All images obtained before and during treatment.
- Treatment characteristics: Dosimetric and planning data, treatment duration per fraction, treatment adaptation mode per fraction, percentages of fractions delivered as planned, visibility and change of contours of the individual lymph nodes on MRI.

2.4. Statistics

The primary study parameter will be presented as a percentage. Missing data is not applicable for this parameter. Since this is a feasibility study, no power calculation has been performed to estimate the required number of patients in this trial.

As the number of patients in this study is relatively low, we assume our data is non-normally distributed. Therefore, continuous variables will be presented as median with inter-quartile range. Non-parametric statistical analyses will be performed on secondary outcome measures (hearing loss and toxicity) to compare baseline scoring with time points after the end of radiotherapy treatment. Time-to-event data (regional recurrence) will be analyzed with the Kaplan-Meier method. PROs and PREMs will be analyzed with a mixed model.

Descriptive statistics will be used for patient, treatment and tumor characteristics at baseline.

2.5. Planned timeline

Primary accelerated fractionation for advanced laryngeal/oropharyngeal/hypopharyngeal cancer for patients with a WHO 0–1 performance status and a N0-1 neck disease was performed in the UMCU in 20 cases in 2021. Based on previous studies conducted in our hospital for HNSCC patients we estimate an accrual rate of 50 %. Therefore, a total of 2 years will be necessary to complete treatment for 20 patients and collect the primary endpoint. An additional 2 years will be necessary to collect all secondary outcomes (regional recurrence, toxicity and patient tolerability). We will start including patients in the first quartile of 2023.

3. Ethics and dissemination

Individual elective lymph node irradiation specifies the radiation dose to the elective targets based on the size of possible occult metastases. Therefore, the dose to the elective neck volumes can be reduced [27]. Patients participating in the iNode study will receive a lower dose to several organs at risk, which could lead to a lower toxicity rate. However, compared to conventional treatment, there might be an increase of regional recurrences. In order to detect possible regional recurrences in an early phase, three additional ultrasound examinations are performed during follow-up. Additionally, patients with a regional recurrence can be treated with post-radiotherapy surgical neck dissection.

The on-table time on the MR-linac will be approximately twice as long compared to conventional treatment (15 vs 30 min). If patients cannot endure the treatment on the MR-linac, it is possible to finish treatment on the conventional linac. Switching to conventional treatment will not have consequences for the treatment outcome.

Hearing protection is provided in compliance with standard procedures, and hearing loss is therefore not expected to occur as a result of the noise exposure caused by the MRI scanner. However, there is little experience with repetitive MR noise exposure in a time span of several weeks as is encountered in the RT schedules of 20 fractions on the MR-linac. One retrospective cohort study describes similar exposure, in which no clinical relevant hearing loss was observed [28]. To ascertain that there is no permanent hearing damage after the repetitive exposure to the MR noise, hearing loss will be closely monitored by an audiologist.

If the iNode trial is proved feasible according to our pre-set criteria and if no unexpected serious adverse events are observed, we will proceed to set up a randomized controlled trial to compare individual elective lymph node irradiation with conventional ENI. The MR-linac consortium, which is a registry-based collaboration between several hospitals worldwide that accommodate an MR-linac, could facilitate to perform this study in a multicenter setting. In this future trial we will further assess the efficacy (i.e. regional recurrence) and benefits (i.e. reduced complications) of this new treatment concept.

Funding statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Registration details

Number of Dutch registry for clinical trials: NL79278.041.22, Ned-Mec protocol number: 22/583, date of approval: 22-06-2022.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2022.100574>.

References

- [1] Baudelet M, Van den Steen L, Tomassen P, Bonte K, Deron P, Huvenne W, et al. Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy. *Head Neck* 2019;41:3594–603. <https://doi.org/10.1002/hed.25880>.
- [2] Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127–36. [https://doi.org/10.1016/S1470-2045\(10\)70290-4](https://doi.org/10.1016/S1470-2045(10)70290-4).
- [3] Boomsma MJ, Bijl HP, Langendijk JA. Radiation-induced hypothyroidism in head and neck cancer patients: A systematic review. *Radiother Oncol* 2011;99:1–5. <https://doi.org/10.1016/j.radonc.2011.03.002>.
- [4] Wilbers J, Dorresteijn LD, Haast R, Hoebbers FJ, Kaanders JH, Boogerd W, et al. Progression of carotid intima media thickness after radiotherapy: A long-term prospective cohort study. *Radiother Oncol* 2014;113:359–63. <https://doi.org/10.1016/j.radonc.2014.10.012>.
- [5] Carpenter DJ, Mowery YM, Broadwater G, Rodrigues A, Wisdom AJ, Dorth JA, et al. The risk of carotid stenosis in head and neck cancer patients after radiation therapy. *Oral Oncol* 2018;80:9–15. <https://doi.org/10.1016/j.oraloncology.2018.02.021>.
- [6] Ramaekers BLT, Joore MA, Grutters JPC, Van Den Ende P, De JJ, Houben R, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. *Oral Oncol* 2011;47:768–74. <https://doi.org/10.1016/j.oraloncology.2011.05.012>.
- [7] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26:3770–6. <https://doi.org/10.1200/JCO.2007.14.6647>.
- [8] Suwinski R, Maciejewski B, Withers HR. Dose-response relationship for elective neck irradiation of head and neck cancer—facts and controversies. *Neoplasma* 1998;45.
- [9] Kaanders JHAM, van den Bosch S, Dijkema T, Al-Mamgani A, Raaijmakers CPJ, Vogel WV. Advances in cancer imaging require renewed radiotherapy dose and target volume concepts. *Radiother Oncol* 2020;148:140–2. <https://doi.org/10.1016/j.radonc.2020.04.016>.
- [10] Van Den Bosch S, Dijkema T, Verhoef LCG, Zwijnenburg EM, Janssens GO, Kaanders JHAM. Patterns of recurrence in electively irradiated lymph node regions after definitive accelerated intensity modulated radiation therapy for head and neck squamous cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2016;94:766–74. <https://doi.org/10.1016/j.ijrobp.2015.12.002>.
- [11] Leeman JE, Li Jg, Pei X, Venigalla P, Zumsteg ZS, Katsoulakis E, et al. Patterns of treatment failure and postrecurrence outcomes among patients with locally advanced head and neck squamous cell carcinoma after chemoradiotherapy using modern radiation techniques. *JAMA Oncol* 2017;3:1487–94. <https://doi.org/10.1001/jamaoncol.2017.0973>.
- [12] Deschuymer S, Nevens D, Duprez F, Daisne J-F, Dok R, Laenen A, et al. Randomized clinical trial on reduction of radiotherapy dose to the elective neck in head and neck squamous cell carcinoma; update of the long-term tumor outcome. *Radiother Oncol* 2020;1–6. <https://doi.org/10.1016/j.radonc.2020.01.005>.
- [13] Maguire PD, Neal CR, Hardy SM, Schreiber AM. Single-Arm Phase 2 Trial of Elective Nodal Dose Reduction for Patients With Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck. *Int J Radiat Oncol Biol Phys* 2018;100:1210–6. <https://doi.org/10.1016/j.ijrobp.2017.12.277>.
- [14] Sher DJ, Pham NL, Shah JL, Sen N, Williams KA, Subramaniam RM, et al. Prospective Phase 2 Study of Radiation Therapy Dose and Volume De-escalation for Elective Neck Treatment of Oropharyngeal and Laryngeal Cancer. *Int J Radiat Oncol Biol Phys* 2021;109:932–40. <https://doi.org/10.1016/j.ijrobp.2020.09.063>.
- [15] Daisne JF, Installé J, Bihin B, Laloux M, Vander Borgh T, Mathieu I, et al. SPECT/CT lymphoscintigraphy of sentinel node(s) for superselective prophylactic irradiation of the neck in cN0 head and neck cancer patients: A prospective phase I feasibility study. *Radiat Oncol* 2014;9:1–9. <https://doi.org/10.1186/1748-717X-9-121>.
- [16] van den Bosch S, Dijkema T, Kunze-Busch MC, Terhaard CHJ, Raaijmakers CPJ, Doornaert PAH, et al. Uniform FDG-PET guided GRADient Dose prEscription to reduce late Radiation Toxicity (UPGRADE-RT): Study protocol for a randomized clinical trial with dose reduction to the elective neck in head and neck squamous cell carcinoma. *BMC Cancer* 2017;17:1–8. <https://doi.org/10.1186/s12885-017-3195-7>.
- [17] De Veij Mestdagh PD, Schreuder WH, Vogel WV, Donswijk ML, Van Werkhoven E, Van Der Wal JE, et al. Mapping of sentinel lymph node drainage using SPECT/CT to tailor elective nodal irradiation in head and neck cancer patients (SUSPECT-2): a single-center prospective trial. *BMC Cancer* 2019;19:1–9. <https://doi.org/10.1186/s12885-019-6331-8>.
- [18] Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014;110:172–81. doi:10.1016/j.radonc.2013.10.010.
- [19] de Ridder M, Raaijmakers CPJ, Pameijer FA, de Bree R, Reinders FCJ, Doornaert PAH, et al. Target Definition in MR-Guided Adaptive Radiotherapy for Head and Neck Cancer. *Cancers (Basel)* 2022;14. <https://doi.org/10.3390/cancers14123027>.
- [20] Reinders FCJ, Stijnman PRS, de Ridder M, Doornaert PAH, Raaijmakers CPJ, Philippens MEP. MRI visibility and displacement of elective lymph nodes during radiotherapy in head and neck cancer patients. *Front Radiol* 2022. <https://doi.org/10.3389/fradi.2022.1033521>.
- [21] Reinders FCJ, van Heijst TCF, Mases J, Terhaard CHJ, Doornaert PAH, Philippens MEP, et al. Magnetic resonance guided elective neck irradiation targeting individual lymph nodes: A new concept. *Phys Imaging Radiat Oncol* 2021;20:76–81. <https://doi.org/10.1016/j.phro.2021.10.006>.
- [22] de Veij Mestdagh PD, Walraven I, Vogel WV, Schreuder WH, van Werkhoven E, Carbaat C, et al. SPECT/CT-guided elective nodal irradiation for head and neck cancer is oncologically safe and less toxic: A potentially practice-changing approach. *Radiother Oncol* 2020;147:56–63. <https://doi.org/10.1016/j.radonc.2020.03.012>.
- [23] Glover GH. Multipoint dixon technique for water and fat proton and susceptibility imaging. *J Magn Reson Imaging* 1991;1:521–30. <https://doi.org/10.1002/jmri.1880010504>.
- [24] Brouwer CL, Steenbakkers RJHM, Bourhis J, Budach W, Grau C, Grégoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. *Radiother Oncol* 2015;117:83–90. <https://doi.org/10.1016/j.radonc.2015.07.041>.
- [25] Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial. *Lancet* 2003;362:933–40. [https://doi.org/10.1016/S0140-6736\(03\)14361-9](https://doi.org/10.1016/S0140-6736(03)14361-9).
- [26] Philippens M, Peltenburg B, Doornaert P, Pameijer F, Kotte A, De Bree R, et al. Head-and-neck tumor delineation for MRI guided adaptive (chemo)radiotherapy. *ESTRO 2020:POSTER-167*.
- [27] van den Bosch S, Vogel WV, Raaijmakers CP, Dijkema T, Terhaard CHJ, Al-Mamgani A, et al. Implications of improved diagnostic imaging of small nodal metastases in head and neck cancer: Radiotherapy target volume transformation and dose de-escalation. *Radiother Oncol* 2018;128:472–8. <https://doi.org/10.1016/j.radonc.2018.04.020>.
- [28] Bongers S, Slottje P, Kromhout H. Hearing loss associated with repeated MRI acquisition procedure-related acoustic noise exposure: An occupational cohort study. *Occup Environ Med* 2017;74:776–84. <https://doi.org/10.1136/oemed-2016-103750>.