Personalized neck irradiation guided by sentinel lymph node biopsy in patients with squamous cell carcinoma of the oropharynx, larynx or hypopharynx with a clinically negative neck: (Chemo)radiotherapy to the PRIMary tumor only. Protocol of the PRIMO study

Bosch, S. van den; Takes, R.P.; Ridder, M. de; Bree, R. de; Al-Mamgani, A.; Schreuder, W.H.; ... ; Kaanders, J.H.A.M.

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Personalized neck irradiation guided by sentinel lymph node biopsy in patients with squamous cell carcinoma of the oropharynx, larynx or hypopharynx with a clinically negative neck: (Chemo)radiotherapy to the PRIMary tumor only. Protocol of the PRIMO study

S. van den Bosch [a,*], R.P. Takes [b], M. de Ridder [c], R. de Bree [d], A. Al-Mamgani [e], W.H. Schreuder [f], F.J.P. Hoebers [g], S. van Weert [h], J.B.W. Elbers [i], J.A. Hardillo [j], T.W.H. Meijer [k], B.E.C. Plaat [l], M.A. de Jong [m], J.C. Jansen [n], D.J. Wellenstein [b], G.B. van den Broek [b], W.V. Vogel [o], A.I.J. Arens [p], J.H.A.M. Kaanders [a]

[a] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Department of Otorhinolaryngology and Head and Neck Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
[c] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[d] Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[e] Department of Radiation Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, The Netherlands
[f] Department of Head and Neck Surgical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, The Netherlands
[g] Department of Radiation Oncology (Maastro), Maastricht University Medical Center+, GROW-School for Oncology and Reproduction, Maastricht, The Netherlands
[h] Department of Otorhinolaryngology and Head and Neck Surgery, Maastricht University Medical Center+, Maastricht, The Netherlands
[i] Department of Radiation Oncology, Erasmus MC Cancer Centre, Rotterdam, The Netherlands
[j] Department of Otorhinolaryngology and Head and Neck Surgery, Erasmus MC Cancer Centre, Rotterdam, The Netherlands
[k] Department of Radiation Oncology, University Medical Center Groningen, Groningen, The Netherlands
[l] Department of Otorhinolaryngology and Head and Neck Surgery, University Medical Center Groningen, Groningen, The Netherlands
[m] Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands
[n] Department of Otorhinolaryngology and Head and Neck Surgery, Leiden University Medical Center, Leiden, The Netherlands
[o] Department of Medical Imaging/Department of Nuclear Medicine, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, The Netherlands
[p] Department of Medical Imaging/Department of Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

Background: Elective neck irradiation (ENI) is performed in head and neck cancer patients treated with definitive (chemo)radiotherapy. The aim is to eradicate nodal metastases that are not detectable by pretreatment imaging techniques. It is conceivable that personalized neck irradiation can be performed guided by the results of sentinel lymph node biopsy (SLNB). It is expected that ENI can be omitted to one or both sides of the neck in 9 out of 10 patients, resulting in less radiation side effects with better quality of life.

Methods/design: This is a multicenter randomized controlled trial aiming to compare safety and efficacy of treatment with SLNB guided neck irradiation versus standard bilateral ENI in 242 patients with cN0 squamous cell carcinoma of the oropharynx, larynx or hypopharynx for whom bilateral ENI is indicated. Patients randomized to the experimental-arm will undergo SLNB. Based on the histopathologic status of the SLNs, patients will receive no ENI (if all SLNs are negative), unilateral neck irradiation only (if a SLN is positive at one side of the neck) or bilateral neck irradiation (if SLNs are positive at both sides of the neck). Patients randomized to the control arm will not undergo SLNB but will receive standard bilateral ENI. The primary safety endpoint is the number of patients with recurrence in regional lymph nodes within 2 years after treatment. The primary efficacy endpoint is patient reported xerostomia-related quality of life at 6 months after treatment.

* Corresponding author at: Radboud University Medical Center, Department of Radiation Oncology, huispost 874, P.O. Box 9101, Nijmegen 6500 HB, The Netherlands.
E-mail address: sven.vandenbosch@radboudumc.nl (S. van den Bosch).

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Discussion: If this trial demonstrates that the experimental treatment is non-inferior to the standard treatment in terms of regional recurrence and is superior in terms of xerostomia-related quality of life, this will become the new standard of care.

1. Introduction/Rationale

Squamous cell carcinoma (SCC) of the upper aerodigestive tract (larynx and pharynx) is associated with a substantial risk of cervical lymph node metastases [1]. Because historically, diagnostic work-up had limited accuracy for the detection of small nodal metastases, bilateral elective irradiation of large anatomical volumes of the neck is performed routinely in the majority of patients receiving definitive (chemo)radiotherapy ((C)RT) [2,3]. The aim is to eradicate nodal metastases that are not detectable by pretreatment imaging techniques (i.e. occult or microscopic metastases) [4]. Most toxicity and permanent long-term radiation side effects are caused by elective neck irradiation (ENI) because the irradiated tissue volume is much larger than what is necessary to treat only the primary tumor. These side effects, and in particular dysphagia and xerostomia, are notoriously known to negatively and permanently affect quality of life [5,6]. The prevalence of occult metastases is approximately 30 % in patients with a clinically negative neck (based on physical examination and imaging) [7]. Therefore, the majority of patients will not benefit from ENI but do carry the burden of consequential radiation sequelae. While current multimodal imaging approaches of the neck have unprecedented accuracy in the detection of small nodal metastases, the sensitivity for the detection of micrometastases is still insufficient to omit ENI [4,8].

Sentinel lymph node biopsy (SLNB) has emerged as a staging procedure that can reliably detect microscopic nodal metastases by meticulous histopathological examination of the sentinel lymph nodes (SLN). The technique is based on the premise that metastases orderly progress with the lymphatic flow from the primary tumor to the SLN before spreading to subsequent draining lymph nodes, and that the pathologic status of the SLN accurately reflects the histology of subsequent lymph nodes [9]. To date, SLNB is not yet performed routinely in patients with larynx and pharynx cancer that are primarily treated with (C)RT. Recently, a systematic review and *meta*-analysis on the diagnostic test accuracy of SLNB in patients with SCC of the oropharynx (n = 162) and larynx/hypopharynx (n = 215) was published [7]. With pooled estimates of sensitivity and negative predictive value of 0.93 and 0.97 respectively, the diagnostic test accuracy was excellent. Identified SLNs were successfully harvested in 98 % of the patients and contralateral SLN(s) were identified in 26 % of the patients. Histopathological analysis of the SLNs was positive in 30 % of the patients.

Based on these results, it is conceivable that personalized neck irradiation can be performed guided by the results of SLNB in patients that receive definitive (C)RT for clinically node negative larynx and pharynx cancer. There are 3 possible scenarios. First, patients will receive no ENI (if all sentinel lymph nodes are negative), unilateral neck irradiation only (if a sentinel lymph node is positive at one side of the neck) or bilateral neck irradiation (if sentinel lymph nodes are positive at both sides of the neck). With this approach, futile bilateral or unilateral ENI can be avoided in approximately 90 % of the patients because occult nodal metastases are only present in 30 % of the patients (of which 75 % unilaterally only) [7]. If proven safe, this will enable better sparing of normal tissues (i.e. parotid and submandibular glands, pharyngeal constrictor muscles, thyroid gland and carotid arteries) from radiation and will likely result in less permanent long-term radiation side effects (i.e. xerostomia, dysphagia, hypothyroidism and carotid atherosclerosis) with better quality of life after treatment compared to standard treatment with bilateral ENI.

The PRIMO trial is designed as a practice-changing multicenter clinical trial to confirm the safety and efficacy of SLNB guided neck irradiation compared to standard bilateral ENI in patients receiving definitive (C)RT for node negative larynx and pharynx cancers.

2. Design

The PRIMO study is a national multicenter, randomized, controlled, phase III trial in The Netherlands.

Adult patients that are planned for definitive (C)RT for newly first diagnosed stage cT1-4N0M0 SCC of the oropharynx, larynx or hypopharynx with indication for bilateral ENI are eligible. Computed tomography (CT) and/or magnetic resonance imaging (MRI) and an 18F-fluoro-deoxy-glucose positron emission tomography ([^{18}F]FDG-PET) confirming cN0-classification prior to inclusion and randomization are mandatory. All in- and exclusion criteria are listed in Table 1.

In total, 242 patients will be randomized in ratio 1:1 to the control or experimental arm. Fig. 1 gives an overview of the trial design. In the control arm, all patients will receive standard bilateral ENI. In the experimental arm, patients will undergo SLNB. Neck irradiation is only performed to the neck side(s) with positive SLN(s) on histopathological examination. To ensure balance between treatment arms, allocation is determined using minimization with a random element [10]. Factors that will be balanced are institution, tumor site, HPV-status in case of oropharyngeal tumors, T-classification and concurrent chemotherapy. During a 2-year follow-up period, data on endpoints will be collected. The trial is positive when the experimental treatment compared to the standard treatment is non-inferior in terms of regional recurrence and is superior in terms of xerostomia-related quality of life.

2.1. Treatment description

Diagnostic work-up will be done in a multidisciplinary fast-track program [11]. This will include physical examination and flexible

Table 1
In- and exclusion criteria.

Inclusion criteria	Exclusion criteria
- Adult patients (≥18 years) with newly diagnosed cT1-4N0M0 SCC of the oropharynx, larynx or hypopharynx. - Histopathological diagnosis of SCC in the primary tumor. - Adequate staging of the neck including CT and/or MRI, and 18F-FDG-PET demonstrating cN0 - Recommendation for curative intent external beam (C)RT made by a multidisciplinary head and neck oncology team (in case of chemoradiotherapy, only concomitant platinum-based regimen are eligible). - Bilateral elective neck irradiation is indicated according to Dutch consensus guidelines (see Table 2). - Procedures for SLNB (i.e. tumor accessible for tracer injection, imaging and surgery under general anesthesia) are deemed feasible by the head and neck surgeon.	- Recurrent disease or previous anticancer treatment to the head and neck area (e.g. radical attempt or tumor reductive surgery, neck dissection, neo-adjuvant chemotherapy or RT) except glottic laser micro surgery. - Well lateralized oropharyngeal cancers and early stage laryngeal cancers requiring no or unilateral elective neck irradiation according to Dutch consensus guidelines - Patients receiving concomitant non-platinum-based systemic agents (e.g. cetuximab). - Compromised airway or tracheostomy. - Proton therapy - Any active invasive malignancy within the last 3 years except for early-stage BCC/SCC of the skin and incidental finding of stage T1N0M0 prostate cancer. - Any somatic, psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol or follow-up schedule.

endoscopy of the upper aerodigestive tract, examination under general anesthesia (if deemed necessary), histological biopsy of the tumor and imaging of the head and neck area with at least [^{18}F]FDG-PET/CT-scan, MRI and/or diagnostic CT. Clinical tumor staging and recommendations for the treatment plan are discussed in a multidisciplinary conference by the head-and-neck oncology team consisting of at least a head and neck surgeon, radiation-oncologist, medical oncologist, radiologist / nuclear medicine physician and a pathologist.

Sentinel lymph node biopsy (experimental-arm only) in this study is based on the procedures described in international consensus guidelines on SLNB in early stage oral cavity cancers [12,13].

To visualize SLNs, the radioactive tracer [^{99m}Tc]Tc-Nanocolloid will be used and can optionally be administered together with the fluorescent tracer indocyanine green (ICG) to form the non-covalent bound multimodal tracer ICG-[^{99m}Tc]Tc-Nanocolloid [14]. A flexible endoscopy guide tracer injection under local anesthesia will be performed in the outpatient clinic [15,16]. If the tumor is accessible via transoral route, a direct tracer injection will be performed (for selected oropharyngeal tumors). The aim is to place four peritumoral injections at each quadrant directly around the macroscopic tumor edges in apparently healthy mucosa and one deep intratumoral injection.

To localize SLNs, SPECT/CT imaging will be acquired at 3–4 h after tracer injection [15]. Approximately 2.2 (mean) and 2.7 (mean) SLNs per patient are expected for oropharyngeal and laryngeal/hypopharyngeal cancers respectively [7,15]. For image reading, SPECT, CT and fused SPECT/CT images are displayed using orthogonal multiplanar reconstruction, maximum intensity projection, and volume rendering. For each neck side independently, visualized radioactive lymph nodes located in first draining echelons (or the most intense accumulating node if this is a different echelon node) are considered SLNs. Identified SLNs will be labelled on SPECT/CT images and cutaneous markings will be placed guided by a portable gamma camera.

Identified SLNs will be surgically harvested under general anesthesia. All nodes in the area of the SLN as identified on SPECT/CT imaging that are radioactive and/or fluorescent (in case of a hybrid tracer) will be excised. The SLNs will be identified by a handheld gamma probe/camera fitted with a high-resolution collimator and by a fluorescence camera system (near-infrared) (if applicable). Only SLNs located in neck levels I, II, III, IV, V, VIa will be harvested during surgery. SLNs located paratracheal (level VIb), retropharyngeal (level VIIa) or retrostyloid (VIIb) will not be harvested during surgery but will receive elective irradiation.

Histopathologic examination of SLNs will include serial step sectioning and staining with hematoxylin-eosin and pan-cytokeratin antibody (AE1/3) [17]. Identified metastases are classified as isolated tumor cells (≤0.2 mm), micro-metastases (>0.2 mm and ≤ 2 mm) or macro-metastases (>2mm) [18]. Histopathologic examination of non-SLNs will be performed by conventional methods.

Radiotherapy is the primary treatment modality in all patients. For radiation treatment planning, a high-resolution CT-scan using an intravenous iodinated contrast agent of the head and neck area will be acquired. The CT-scan will extend from at least the level above the base of the skull to below the clavicles with a maximum slice thickness of 3 mm. A custom-made thermoplastic head, neck and shoulders mask is used to immobilize the patient during the scanning procedure and during radiotherapy. Co-registration with other diagnostic imaging (e.g. MRI and PET) will be performed to facilitate delineation of target volumes.

The primary tumor will always be irradiated, independent of randomization. The gross target volume (GTVp) of the primary tumor will be delineated on the planning CT-scan and will encompass all overtly macroscopic disease using information from clinical examination and diagnostic imaging. To cover all routes of potential microscopic tumor infiltration, two clinical target volumes (CTV) will be created by expansion of the GTVp (i.e. CTVp1 and CTVp2 corresponding to a high and lower subclinical tumour burden) using the concept as documented in the international consensus guideline by Gregoire et al [19].

Treatment of the neck is dependent on randomization. For patients randomized to the control-arm, standard bilateral ENI will be performed. Selection of neck levels will be performed according to Dutch consensus guidelines (Table 2). In short, elective treatment of bilateral neck levels II, III and IV is indicated in all patients. Based on extension of the primary tumor, elective irradiation of additional neck levels can be mandatory. The CTV elective (CTVe) will be delineated according to international consensus guidelines by Gregoire et al [3]. For patients randomized to the experimental-arm, neck irradiation will be performed

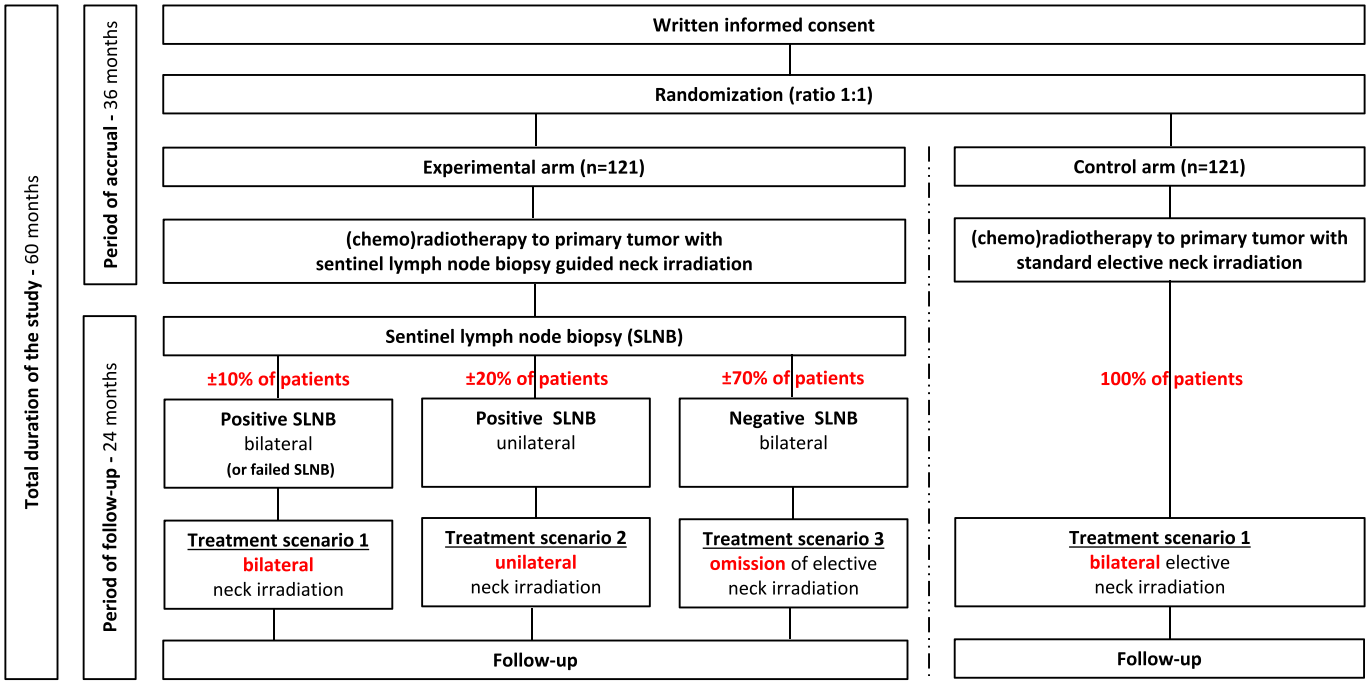

Fig. 1. Overview of the trial design.

Table 2
Dutch consensus guidelines for selection of neck levels for elective irradiation.

Selection of neck levels for elective irradiation
In The Netherlands, the Dutch national consensus guidelines of the 'Landelijk platform radiotherapie voor hoofd-hals tumoren (LPRHHT)' of the 'Dutch Society for Radiation Oncology (NVRO)' on target volume selection for elective neck irradiation are applied in patients receiving curative (chemo)radiotherapy for oropharyngeal, laryngealor hypopharyngeal squamous cell carcinoma.
No elective neck irradiation will be performed for early-stage laryngeal cancers without impaired vocal cord mobility and without subglottic extension (i.e. cT1-2aN0 glottic or cT1N0 supraglottic cancers). Elective neck irradiation may also be omitted in small tonsillar / soft palate cancers (cT1N0).
Unilateral elective neck irradiation will be performed for well lateralized oropharyngeal cancers (i.e. extension in the soft palate to at most the lateral 2/3 of the hemi structure and > 1 cm from midline, extension in the tongue base to at most the lateral 1/3 of the hemi structure and at most 1 cm and clinically classified cN0-2b.
Bilateral elective neck irradiation will be performed in all other cases and will include:
- Level II, III and IVa (bilateral) in all cases.
- Level Ib (unilateral) when the tumor extends in the oral cavity (retromolar trigone, mobile tongue,gum, or oral side of the anterior tonsillar pillar).
- Level IVb (unilateral) in case of pathologic lymph node(s) in level IVa.
- Level Va + b (unilateral) in case of pathologic lymph nodes(s) in any level.
- Level VIa (bilateral) when the tumor extends through the anterior outer cortex of the thyroid cartilage.
- Level VIb (bilateral) when the tumor extends in the subglottic area, post cricoid area, esophagus or in the apex of the pyriform sinus.
- Level VIIa (retropharyngeal) (bilateral) when the tumor extends in the posterior pharyngeal wallor is transfixing the soft palate.
- Level VIIb (retrostyloid) (unilateral) in case of pathologic lymph node(s) > 3 cm in diameter in level II or pathologic lymph node(s) in upper level II (located at the level cranial to the upper half of the second cervical vertebra).

or (partially) omitted based on the results of SLNB. Lymph drainage patterns as visualized on SPECT/CT will be taken into account. The flowchart in Fig. 2 and an example of radiation dose planning in Fig. 3 give an overview of neck irradiation in the experimental-arm. Indication for neck irradiation is determined for each side of the neck separately. In short, ENI is omitted to neck sides with negative SLNB. Contralateral ENI is also omitted in case of unilateral lymph drainage is visualized on SPECT/CT (and per protocol tracer injection was performed) [20]. Neck levels with SLNs visualized on SPECT/CT that were not harvested during surgery will be irradiated. If neck irradiation is indicated, the CTVe will be delineated according to the international consensus guidelines by Gregoire et al [3].

Patients will be treated with external beam radiotherapy using a volumetric-modulated arc therapy (VMAT) or equivalent, with simultaneous integrated boost (SIB) technique to deliver multiple dose levels. The aim is to start radiation treatment within 30 days after first consultation. Position verification with online cone beam CT-scan (CBCT) will be performed during treatment to verify correct positioning of the patient prior to each fraction. Dose prescribed to the primary tumor will be equivalent to at least 70 Gy in 2.00 Gy fractions in 7 weeks (PTV of CTVp1). Dose prescribed to the elective volume will be equivalent to at least 44 Gy in 2.00 Gy fractions in 4.5 weeks (PTV of CTVp2 and CTVe). At least 99 % of the PTV volumes will receive ≥ 95 % of the prescribed dose. For the boost volume, the mean dose will be at least the prescribed dose and the maximum dose will be ≤ 107 % of the prescribed dose. The planning objective for normal tissues is to deliver an as low as reasonably achievable dose to the salivary glands (parotid and submandibular glands), oral cavity, pharyngeal constrictor muscles (superior, middle and inferior), thyroid gland and carotid arteries. Patients with locally advanced disease (cT3-4) may be treated with concomitant chemoradiotherapy according to local institutional protocols. Patients will receive either cisplatin (weekly 40 mg/m2 or 3-weekly 100 mg/m2) or carboplatin-based regimens (weekly with AUC 1.5) if unfit for cisplatin.

Standard oncologic follow-up after radiotherapy will be performed. This will include physical examination and flexible endoscopy of the upper aerodigestive track and examination of the neck by palpation. Only for patients randomized to the experimental arm, routine ultrasound of the neck is performed every 4–6 months until 2 years after end of treatment. If a recurrence is suspected during follow-up, additional imaging is acquired (e.g. MRI, CT, PET or US) and biopsy for cytological or histological confirmation is performed. In case of recurrence, patients are again evaluated by the multidisciplinary head and neck oncology

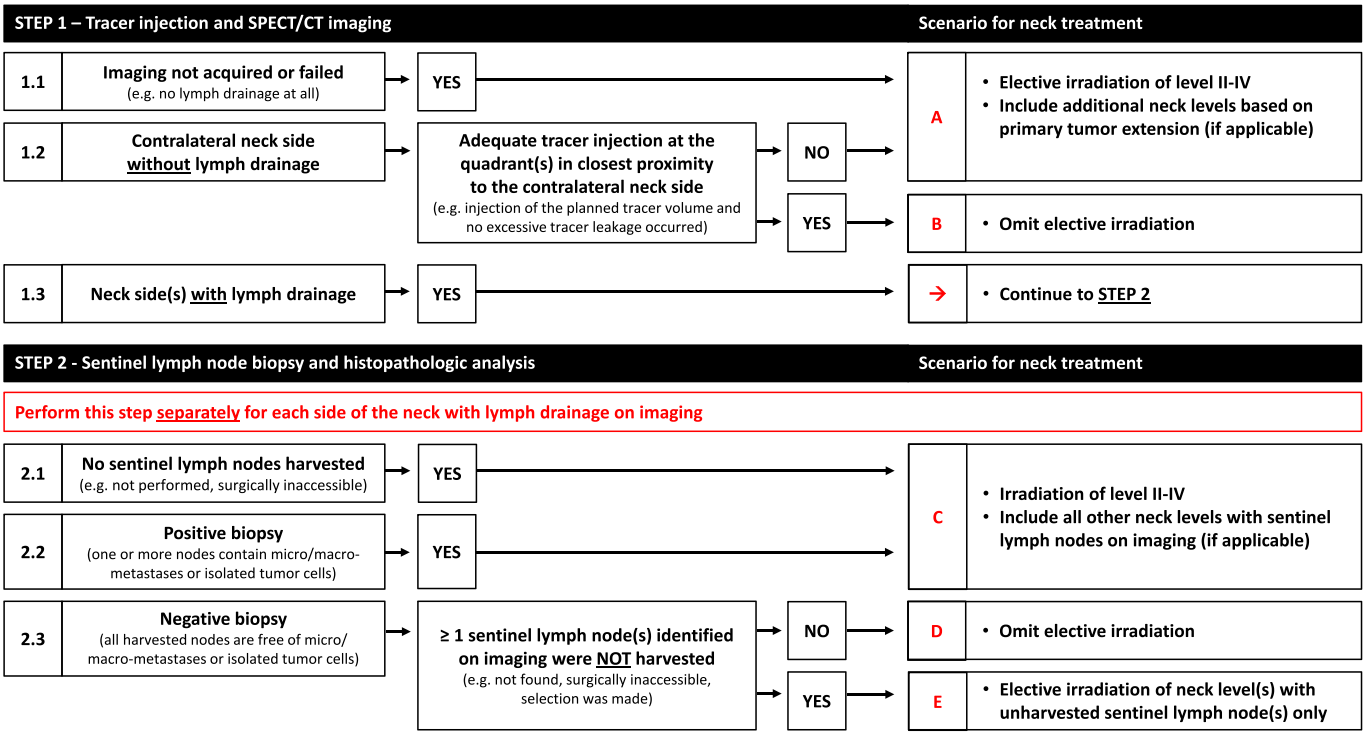

Fig. 2. Overview of neck irradiation in the experimental-arm.

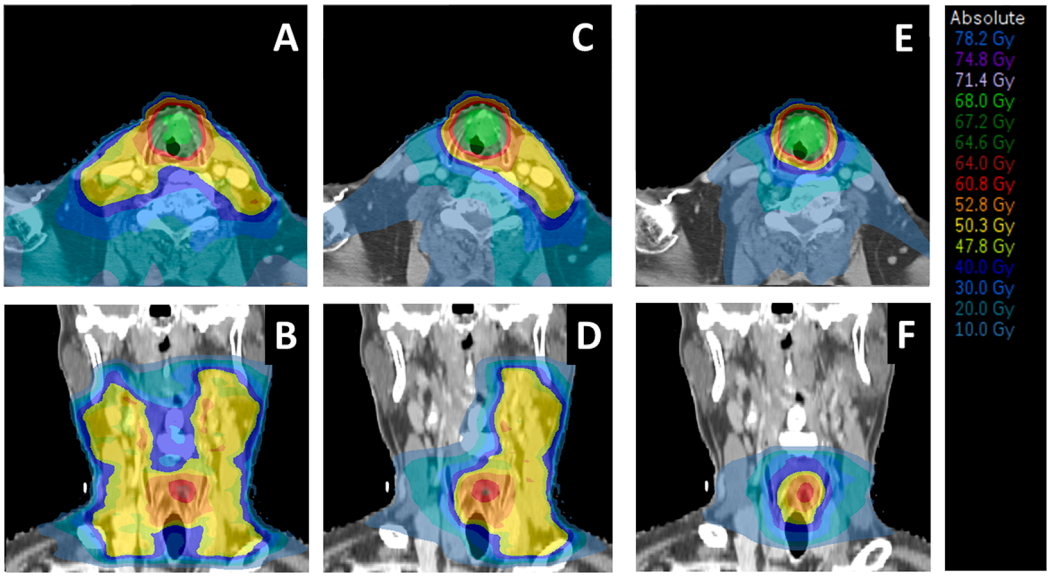

Fig. 3. Radiation dose planning in the experimental-arm. Transverse and coronal views of radiation dose planning with bilateral (A-B), unilateral (C-D) and no neck irradiation (E-F) for a case with cT3N0 laryngeal cancer, illustrating the major dosimetric gains to uninvolved tissues with sentinel lymph node biopsy guided neck irradiation.

team for further management.

Assessment of outcomes in the context of this trial will be performed until 2 years after treatment. Table 3 gives an overview of when and what outcomes will be assessed.

Acute and late treatment associated toxicity will be scored according to the common toxicity criteria of adverse events (CTCAE) v5.0 by the radiation oncologist at each follow-up visit. Additionally, the patient's weight and the presence and duration of tube feeding will be documented.

General quality of life will be evaluated using the self-administered EORTC QLQ-C30, QLQ-HN35 and EQ-5D-5L questionnaires [21–23]. In-depth evaluation of xerostomia-related quality of life will be performed using the self-administered Groningen Radiotherapy-Induced Xerostomia questionnaire (GRIX) [24]. Assessment of swallowing function will be performed by trained study personnel. Functional performance will be scored using the Performance Status Scale for Head & Neck Cancer Patients (PSS-HN) [25]. The PSS-HN is a clinician rated instrument and is designed to evaluate performance in areas of functioning most likely affected by head and neck cancer and its treatment. The following domains are evaluated: normalcy of diet, eating in public and understandability of speech. For quantitative evaluation of the swallowing function, the water swallowing test (WST) will be used [26]. The WST is a simple swallowing performance measure (swallow volume, capacity and speed will be registered) to monitor change over time. Dysphagia-related quality of life will be evaluated using the self-administered Swallowing Quality of Life Questionnaire (SWAL-QOL) [27].

Assessment of thyroid gland function will be performed by blood analysis of thyroid stimulating hormone (TSH) and free thyroxin (FT4).

Costs on medical consumption will be assessed using the patient-administered iMTA Medical Consumption Questionnaire (iMCQ) [28]. The iMCQ includes questions related to frequently occurring contacts with health care providers. The patient-administered iMTA Productivity Cost Questionnaire (iPCQ) will be used to measure productivity losses [29]. The iPCQ includes three modules measuring productivity losses of paid work due to absenteeism, presenteeism and productivity losses related to unpaid work. The iPCQ and iMCQ are complimentary and can be used in every indication as they are generic questionnaires.

Table 3
Overview and schedule of procedures regarding outcome assessment.

Procedure	Prior to treatment	During radiotherapy	Months after (chemo)radiotherapy						
			2–3	3–4	6	8–9	12	18	24
Assessment of acute toxicity (CTCAE)	•	•	•						
Assessment of late toxicity (CTCAE)	•		•		•		•	•	•
Assessment of xerostomia									
- xerostomia-related QoL (QLQ-H&N35, GRIX)	•		•		•		•		•
Assessment of dysphagia									
- functional performance (PSS-HN, WST)	•		•		•		•		•
- dysphagia-related QoL (SWAL-QoL)	•		•		•		•		•
Assessment of thyroid gland function									
- blood analysis (TSH, FT_4)	•				•		•	•	•
Assessment quality of life									
- general QoL (QLQ-C30, EQ-5D-5L)	•		•		•		•		•
Routine evaluation of regional recurrence with ultrasound of the neck †				•		•	•	•	•
Assessment of costs and productivity									
- medical costs (iMCQ)		• ∞	• ∞		•		•		•
- productivity (iPCQ)			•		•		•		•

† Routine ultrasound of the neck will be performed in experimental-arm only.
∞ Medical costs during treatment and in the period of recovery will be collected from the patients file in retrospect.

2.2. Endpoints

The PRIMO study has two primary endpoints. The primary safety endpoint is the number of patients with recurrence in regional lymph nodes (in the absence of synchronous recurrence of primary tumor or second primary head and neck tumor) within 2 years after treatment. The primary efficacy endpoint is patient reported xerostomia-related quality of life measured by the xerostomia symptom scale of the EORTC QLQ-H&N35 questionnaire at 6 months after treatment.

Secondary endpoints are times to recurrence (local, regional, loco-regional, and distant), survival times (overall, disease-specific, and disease-free), acute and late radiation toxicity, quality of life, quality adjusted life years and costs.

2.3. Statistics

The sample size for the primary safety outcome is determined on the basis of the hypothesis of non-inferiority of the 2-year regional recurrence rate with an α of 0.025 (one-tailed test) and a power of 0.9. The expected regional recurrence rate is 2.0 % in the control group and 3.1 % in the experimental group [7,30,31]. Assuming that the difference between groups should not exceed 8 %, a total of 220 patients are required when randomizing in ratio 1:1. Anticipating on a drop-out rate of 9 %, a total of 242 patients need to be accrued.

For the primary efficacy outcome a power calculation has been performed for the sample size n = 220 that was calculated for the primary safety outcome. Based on a two-sided two-sample *t*-test with a significance level of 0.05 and under the assumption of a difference of 10 points between the arms and a standard deviation of 23 in both arms, the power of the test is 0.89.

The trial is successful when both safety and efficacy of the experimental treatment is demonstrated. The power of the whole testing procedure (consisting of two tests) is expected to be at least 0.80 (0.9 x 0.89). The analysis will be 'intention to treat'.

An independent Data Safety Monitoring Board (DSMB) consisting of a radiation oncologist, head and neck surgeon and a statistician will be installed to monitor progression of the study and specifically the number of events for the primary safety outcome (ongoing safety surveillance). Events on the primary safety outcome will be reported as serious adverse events (SAE) during the complete period of study participation and will therefore be subject to rapid reporting. The DSMB will have unblinded access to all data and can advise on termination of the study when an unexpected higher number of events for the primary safety outcome is detected in the experimental-arm.

2.4. Quality assurance

A training course for office-based flexible endoscopic SLNB tracer injection was organized on September 20th 2023. The course was attended by a radiation oncologist and a head and neck surgeon of all participating centers. All centers already have experience with taking office-based flexible endoscopic biopsies under local anesthesia and some already have experience with flexible endoscopic SLNB tracer injection. The additional skills required for tracer injection is limited when already performing biopsies. The aim of the training course was equalize know-how and skills between centers and consisted of a theoretical part and a practical hands-on course on fresh frozen human cadavers to train flexible endoscopic SLNB tracer injection.

2.5. Planned timeline

Patient accrual is planned to start in Q4 2023. The anticipated duration of accrual is 3 years. During a 2-year follow-up period, data on endpoints will be collected. Mature data is thus expected in Q4 2028 after which final data analysis can be performed.

Ethical and legal considerations

This PRIMO study will be conducted in accordance with the ethical principles for medical research involving human subjects as stated in the Declaration of Helsinki, ICH-GCP, and the applicable laws and regulations of the Netherlands. Written informed consent will be obtained for each participant. The study was reviewed and approved by the Medical Research Ethics Committee 'METC Oost Nederland' on August 9th 2023 (ID: 2023–16491).

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Trial registration

The PRIMO study is registered at clinicialtrials.gov under the identification NCT05333523. The related information was first posted on April 19th, 2022.

CRediT authorship contribution statement

S. van den Bosch: Conceptualization, Methodology, Funding acquisition, Writing - original draft. **R.P. Takes:** Conceptualization, Writing – review & editing, Funding acquisition. **M. de Ridder:** Writing – review & editing, Funding acquisition. **R. de Bree:** Writing – review & editing. **A. Al-Mamgani:** Writing – review & editing, Funding acquisition. **W.H. Schreuder:** Writing – review & editing. **F.J.P. Hoebers:** Writing – review & editing, Funding acquisition. **S. van Weert:** Writing – review & editing. **J.B.W. Elbers:** Writing – review & editing, Funding acquisition. **J.A. Hardillo:** Writing – review & editing. **T.W.H. Meijer:** Writing – review & editing. **B.E.C. Plaat:** Writing – review & editing. **M. A. de Jong:** Writing – review & editing, Funding acquisition. **J.C. Jansen:** Writing – review & editing. **D.J. Wellenstein:** Writing – review & editing. **G.B. van den Broek:** Writing – review & editing. **W.V. Vogel:** Writing – review & editing. **A.I.J. Arens:** Conceptualization, Writing – review & editing. **J.H.A.M. Kaanders:** Conceptualization, Methodology, Funding acquisition, Writing – review & editing, Supervision.

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.

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