


STUDY PROTOCOL

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DeintensiF: Standard versus individualized deintensified follow-up after curative treatment in head and neck cancer: protocol of a randomized pilot study

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Abstract

Background Around 70% of head and neck cancer (HNC) cases are diagnosed in an advanced stage. Improvements in treatment have led to a cure rate of up to 80–90% for early-stage and 40–50% for advanced-stage disease. However, routine follow-up involves social and financial burdens, including frequent imaging associated with radiation exposure and costs. Currently, there is no consensus on the follow-up strategy after HNC treatment, and no conclusive evidence shows a survival advantage for routine follow-up over symptom-driven self-referrals. The DeintensiF study aims to provide robust evidence, comparing standard follow-up with a tailored deintensified approach. Additionally, it seeks to explore whether early detection of recurrence/second primary malignancy in asymptomatic patients impacts survival and quality of life. The pilot phase aims to assess feasibility of patients' recruitment and adherence to the assigned follow-up strategy and patient-reported outcomes (PROs) questionnaire in the first 2 years.

Methods This randomized-controlled, multicenter, open-label, pilot study has the goal to randomize a minimum of 16 patients across three Swiss sites into two arms within 1 year. The Experimental Arm A: scheduled clinical exams every 6 months and monthly PRO with evaluation and possibility to alert for open urgent appointments; and the Control Arm B: regular visits every 3 months for the first 2 years and less frequent thereafter plus multiple scheduled imaging appointments for head and neck magnet resonance imaging (MRI) and computed tomography (CT) with contrast and chest CT scans. Patients' motivation for participation or not will be explored by additional questionnaire before randomization. The primary objective during the pilot phase is to evaluate the feasibility of recruiting and randomizing patients with complete remission 6 months after treatment of head and neck squamous cell carcinoma to a deintensified and to a conventional follow-up. The secondary objective is to assess adherence to the two different follow-up strategies.

Discussion If feasible, the DeintensiF pilot study will expand from the recruited patients (detailed in the "Methods" section) to a larger cohort of advanced HNC cases in the main trial, integrating electronic PRO tailored follow-up care.

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This approach aims to reshape follow-up practices, enhancing patient-centered strategies and outcomes in head and neck oncology.

Trial-registration ClinicalTrials.gov (NCT05388136); Swiss National Clinical Trial Portal (SNCTP000005198).

Keywords Follow-up studies, Head and neck neoplasms, Squamous cell carcinoma of head and neck, Neoplasm recurrence, Local, Recurrence, Precision medicine, Patient-reported outcome measures

Background and rationale

Head and neck squamous cell carcinoma (HNSCC) are the 6th most common type of non-skin cancer [1]. Tobacco, alcohol, and human papillomavirus (HPV) are the main risk factors. Treatment options vary from surgery to radiotherapy (RT), either alone or combined with chemotherapy (CXRT), tailored to cancer site and stage. Early-stage HNSCC (stages I–II, 30% of cases) typically receive single-modality treatment, while advanced cases (stages III–IVA/B, 70% of cases) often necessitate multimodal approaches, such as CXRT or surgery followed by adjuvant (CX)RT. Cure rates for early-stage cancer reach 80–95%, yet locoregional recurrence (REC) affects 50–60% of advanced cases within 2 years, with 20–30% developing distant metastases. Additionally, there is a +2–4%/year risk of second primary malignancies (SPM), mainly in the lung (60%) and superior aero-digestive tract (20%). HPV-positive oropharyngeal cancer patients exhibit lower REC/SPM risks [2–9]. The 5-year overall survival rates for HNSCC patients treated between 2002 and 2006 averaged 65.9% [10]. Despite treatment successes, patients face treatment-related morbidities, impacting their quality of life (QoL), necessitating comprehensive follow-up (FU) protocols. Curative setting patients' FU in this population includes treatment

response evaluation, REC/SPM detection, management of treatment sequelae, nutritional restoration, and psychosocial support [11]. Unnecessary investigations that may cause morbidity, discomfort, or stress and may add financial burden on the patient need to be avoided. There is neither consensus nor level one evidence on how to ideally achieve these globally accepted FU goals. Guidelines recommend routine clinical visits for head and neck examination, assessing radiation-induced toxicity and functional rehabilitation [12]. Following baseline imaging (magnet resonance imaging (MRI) and computed tomography (CT)) within 3–4 months post-surgery or after definitive CXRT, long-term reimaging until and beyond 5 years in asymptomatic patients remains controversial and unexplored. Within 3–6 months post-CXRT, a hybrid positron emission tomography CT or MRI (PET) is recommended for treatment response assessment and detection of tumor persistence/progression [13]. A chest CT scan should be performed if chest imaging is requested (chest X-ray detects only 33% of intrathoracic lesions visualized by chest CT) [14]. Existing FU approaches lack consensus, varying in visit frequency, imaging, and duration, as listed in Table 1 [15–25].

Routine surveillance has shown survival benefits in two retrospective studies for REC diagnosed during

Table 1 Published guidelines on FU intervals

Period	Year 1	Year 2	Year 3	Year 4	Year 5	> 5 years
Guidelines						
ASHNS (ASHNS, 1999) [15]	1–3	2–4	3–6	4–6	4–6	12
BAHNO (BAHNO, 2001) [16]	1–1.5	1–1.5	3	6	6	12
DCHNO (DCHNO, 2002) [17]	2	3	4	6	6	–
Lester and Wight, 2009 [18]	1	2	3	4	6	12
Digonnet et al., 2013 [12]	2–3	2–3	3–6	3–6	6	12
AIMO/AIRO (AIMO/AIRO, 2016) [19, 20]	1–3	3	3–6	6	6	12
FOS (FOS, 2016) [21]	2	3	4	6	6	12
SSORL (SSORL, 2019) [22]	1–3	1–3	4–6	4–6	4–6	(12)
EHNS/ESMO/ESTRO (EHNS/ESMO/ESTRO, 2020) [23]	2–3	2–3	6	6	6	12
NCCN (NCCN, 2024) [24]	1–3	2–6	4–8	4–8	4–8	12

Suggested interval of FU visits in months by selected authors and national committees

AIMO Associazione Italiana Oncologia Medica, AIRO Associazione Italiana Radioterapia Oncologica, ASHNS American Society of Head and Neck Surgeons, BAHNO British Association of Head and Neck Oncologists, DCHNO Dutch Cooperative Head and Neck Oncology Group, EHNS European Head and Neck Society, ESMO European Society for Medical Oncology, ESTRO European Society for Radiotherapy and Oncology, FOS French ORL Society, NCCN National Comprehensive Cancer Network, SSORL Swiss Society of Oto-Rhino-Laryngology, Head and Neck Surgery

scheduled FU visits compared to self-referral [26, 27]. However, many other retrospective studies found no difference in overall survival (OS) between routine FU and symptom-driven self-referral, indicating that patients efficiently detect symptomatic REC while silent RECs are rare [28–42]. Additionally, electronic Patient-Reported Outcomes (ePROs) enable real-time symptom monitoring and may offer a survival benefit. Basch et al. (2016) demonstrated that web-based ePROs significantly enhanced 1-year survival rates for advanced solid cancer patients [43]. Another study showed that ePROs during chemotherapy for advanced lung cancer increased 2-year survival, surpassing standard post-treatment imaging for REC detection [44]. With limited evidence on post-treatment FU for HNSCC patients, a multicenter trial comparing deintensified and conventional FU strategies is crucial to establish a cost-efficient, patient-centered approach.

The DeintensiF main trial hypothesizes that a patient-centered deintensified and individualized FU strategy is non-inferior compared to a standard FU approach. The specific primary aim of the DeintensiF trial is to determine whether the new approach with enhanced patient involvement actually reduces the number of outpatient visits without compromising survival compared to a standard FU with fixed scheduled clinical exams and imaging in curatively treated HNSCC patients. Secondary objectives relate to investigating additional clinical and economic effects of the deintensified individualized FU scheme. In addition, we aim to disentangle underlying mechanisms and to describe implementation aspects including acceptance and patient views. For the full protocol, see Additional file 1: DeintensiF-Full Protocol.

The general aims of the DeintensiF pilot phase are to evaluate the feasibility of recruiting and randomizing

patients with complete remission 6 months after treatment of HNSCC to a deintensified or conventional (standard) FU. The secondary objective is to investigate adherence to the two different FU strategies. Good compliance is defined as the realization of the planned/organized visits and exams at the planned time ± 4 weeks as well as regularly recording of signs and symptoms in the PROs questionnaire.

Methods

Trial design

Patients fulfilling the eligibility criteria are randomized to one of two FU schedules using a 1:1 ratio. The study also investigates patients' adherence to the assigned protocol and collects additional data on patients' motivation for study participation. Three Swiss academic tertiary referral centers in Bern, Lucerne and Zurich are involved in this initial phase. During the pilot phase, the sites committed to enroll a total of 20 patients within the first year. This phase serves as a crucial precursor to the main trial, providing insights into the practicality and effectiveness of the deintensified FU strategy compared to the standard approach. The pilot study differs from the main study by collecting additional data concerning patients' motivation for study participation and the use of paper-based symptom reporting in the experimental arm (as opposed to an electronic patient-reported outcome data capture system). Otherwise, all procedures mimic the main trial. Data from this pilot study will be used to inform the planned large-scale main trial. Decisions will be based on a traffic light system (Fig. 1) before implementation of the larger-scale main trial, demonstrating its feasibility and relevance in addressing the challenges of post-treatment FU in HNSCC patients [45].

Traffic light*	Enrolment rate	Adherence
Green	≥ 16 participants/year in two best enrolling sites	And $\geq 50\%$ completeness (of all checklists) in recording signs and symptoms in experimental arm and adherence to the assigned FU scheme
Yellow	≥ 12 participants/year in two best enrolling sites	And $\geq 40\%$ completeness (of all checklists) in recording signs and symptoms in experimental arm and adherence to the assigned FU scheme
Red	< 12 participants/year in two best enrolling sites	Or $< 40\%$ completeness (of all checklists) in recording signs and symptoms in experimental arm and adherence to the assigned FU scheme

Fig. 1 Traffic light system for moving from the pilot phase to the main phase. *Green: continue (i.e., no concerning issues that threaten the success of the trial); yellow: either adapt or continue with caution (i.e., remediable issues); red: stop or at least halt (i.e., intractable issues that cannot easily be remedied). Although it is foreseen to have only two to three sites in the pilot, using enrolment in the two best enrolling sites allows also for more sites in the pilot

The success of the pilot study and its progression to the main trial depend on observed enrolment rates and adherence to the FU protocol, as demonstrated in Fig. 2. The criteria for advancing to the main trial are based on the number of sites planned for participation, the size and duration of participation of those sites, and an expected enrolment of 550 patients within 3 years for the main trial.

Objectives and success criteria of the pilot study

Primary objective

The primary objective is to assess the feasibility of recruiting and randomizing HNSCC patients in complete remission 6 months post-treatment to either a deintensified or a conventional FU protocol. The aim is to recruit at least 80% of the committed 20 patients ($n = 16$) within the initial 1-year recruitment period, ensuring that enrollment remains on track to achieve sample size and timeline goals.

Secondary objective

The secondary objective is to investigate adherence to the two FU strategies, defined as the completion of scheduled visits and exams as planned, along with regular recording of signs and symptoms in the patient-reported outcomes (PRO) questionnaire. Good compliance is defined as the realization of the planned/organized visits and exams at the planned time ± 4 weeks as well as regularly recording

of signs and symptoms in the PRO questionnaire. A retention target of 90% is set for those completing scheduled FU assessments, alongside an adherence goal of 85% to the FU schedule. To ensure the reliability of the findings, at least 95% completeness is aimed in required data fields, with data audits conducted by the Clinical Trials Unit at the University of Bern.

Endpoints of the pilot study

Eligibility rate: proportion of all eligible patients out of all screened patients. Consent rate: Proportion of consenting patients among all eligible patients. Patient motivation for participation based on a participation questionnaire. Overall accrual per month and adherence to the randomized FU schedule.

Meeting the targets will confirm the feasibility of moving forward with the main trial. If any challenges arise in recruitment, retention, or data quality, insights from the pilot phase are used to adjust and optimize the approach.

Study procedure

Participants and recruitment

Inclusion criteria.

Participants must be aged 18 or older, have a histopathologically proven invasive HNSCC at clinical/radiological stage II–IV (non-surgically treated) or pathological stage II–IV (surgically treated, excluding M1) according to the

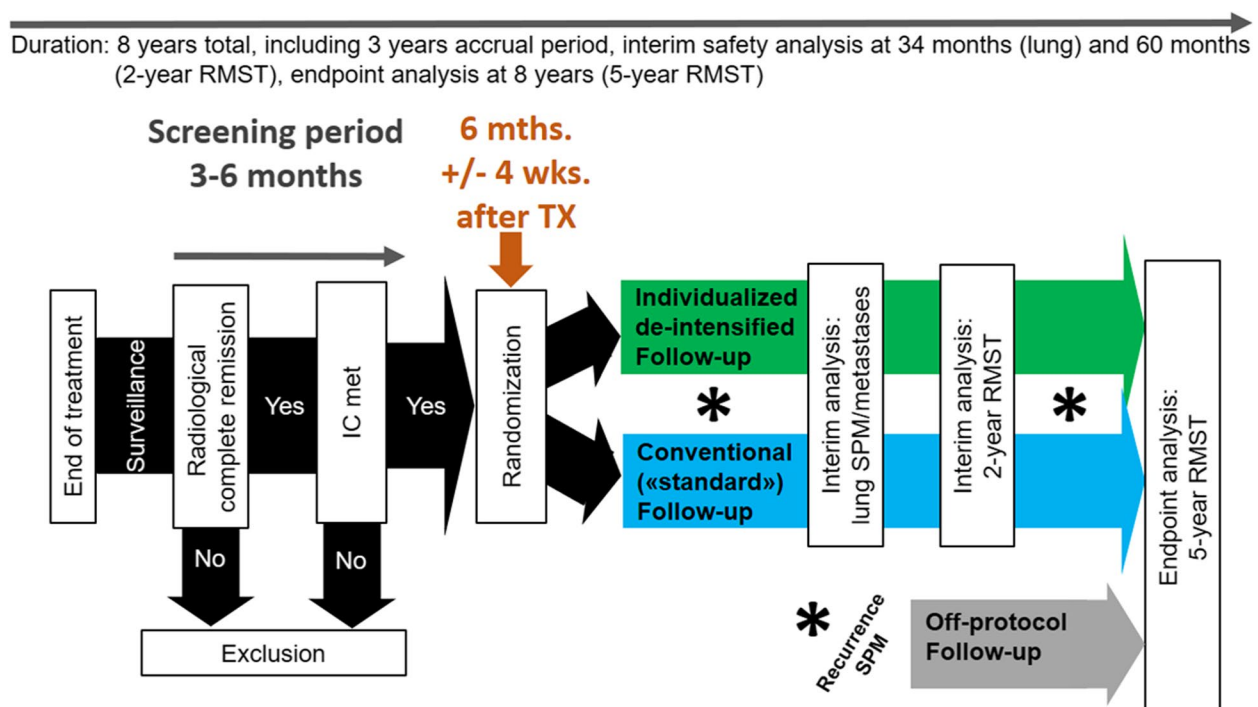


Fig. 2 Flow chart of participants' recruitment and study procedure of the main trial. Abbreviations: IC = inclusion criteria; mths. = months; RMST = restricted mean survival time; SPM = second primary malignancy; TX = treatment; wks. = weeks

Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) UICC/TNM 8th edition. Other inclusion criteria are curative treatment intent, planned FU at the study center, radiological and clinical confirmation of complete remission, and agreement for 5-year FU. Furthermore, signed, written informed consent is required.

Exclusion criteria.

Participants with initial clinical stage I and/or M1 HNSCC, nasopharyngeal cancer or carcinoma of unknown primary, previously treated head and neck cancer (except specified cases), other synchronous or metachronous malignancies (except specified cases), participation in conflicting studies, pregnant or breastfeeding women, and those with conditions affecting protocol compliance will be excluded [46].

For detailed criteria and procedures, refer to the full protocol submitted as supplementary material (see Additional file 1: DeintensiF-Full Protocol).

Recruitment procedure

Patients receive study information through a recruitment flyer and complete a participation questionnaire from the treating centers. Patient registration and randomization are performed online in secuTrial®, with eligibility checks and signed consent obtained.

Randomization and stratification

Following the entry of baseline information and eligibility criteria, participants will be randomized in secuTrial®. They will be assigned to either the experimental (individualized deintensified FU) or control (conventional FU) arm in a 1:1 ratio. Stratification is done via probabilistic minimization to balance prognostic factors across arms [47, 48]. Stratification factors include tumor stage, treatment modality and trial site.

Study intervention

Patients in the experimental arm will have scheduled outpatient visits every 6 months including a clinical examination. In-between, patients complete a monitoring questionnaire monthly, with alerts triggering additional visits, if necessary. Details of the instrument are shown in Table 2. Participants will receive reminders to complete the PROs questionnaire the day before the expected date with up to three reminders in the main study, if missed. During the pilot study, phone calls are conducted if the PROs questionnaire is completely or partially missing 1 day after the planned date, which mimics the automated alert by the app in the future main study. In the main trial, a phone call will also follow 3 days after the app's notification, in case the questionnaire is still not completed. Patients not able to adequately use the app will be offered a paper-based version of the PROs questionnaire, similar to the pilot study.

The use of a paper-based PRO questionnaire in the pilot study is a logistical choice intended to simulate the future electronic alert system. This change is solely for feasibility assessment, and any potential differences in data collection methods will be controlled in subsequent subgroup analyses. If a patient fails to complete the PRO, up to two calls are made within 1 week to gather the results. Depending on the rating, the PRO will trigger an alert, manually by phone call during the pilot phase or automatically through an electronic alert in the main study. The alert will recommend an earlier control visit if the patient's conditions indicate a possible REC/SPM, with the center scheduling an "open urgent appointment" within 2 weeks.

Patients in the control arm will have scheduled outpatient visits with clinical examination every 3 months (years 1–3) and every 6 months (years 4–5). In addition, patients will undergo scheduled imaging 6 and 18 months after enrollment. Smokers will have additional chest CT-scans 30, 42, and 60 months after enrollment. In the conventional arm, participants will also complete the PROs questionnaire monthly and during every visit, but neither participant calls will be made nor alerts will be sent.

Detailed study procedure

The timing of FU visits and the assessments for participants in both arms (conventional FU and individualized deintensified FU) are outlined in Table 3.

Participants will undergo comprehensive imaging, including head and neck MRI or CT scans and contrast-enhanced trunk CT scans, at 3 to 6 months, and at 6 and 18 months post-randomization, to confirm remission and detect secondary primary malignancies (SPM). Annual low-dose chest CT scans without contrast will be performed on current or recent heavy smokers from 18 months to 5 years, per National Comprehensive Cancer Network (NCCN) Guidelines [13, 24]. Adverse events will be monitored using Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Medical interactions, including unscheduled visits and supportive treatments, will be recorded via a Concomitant Care Questionnaire. Compliance with FU visits and symptom monitoring using paper or electronic PRO questionnaires will be tracked. Health care utilization costs, including FU visits, imaging, and personnel expenses, will be documented.

Fear of REC assessment

Fear of REC is assessed monthly using a single-item screening question developed by Rogers et al. (2015) [49], which rates fear on a scale from 0 to 4 [50]. The English version was translated and back translated to German following European Organisation for Research and Treatment of Cancer (EORTC) standards achieving consensus on the final version.

Table 2 Patient reported outcome questionnaire (symptom tracker)

		Answers				
1.	Weight Insert the current weight on the left (use always the same scale at home and under the same conditions) and check on the right whether the weight loss was desired or undesired	(kg)		Weight loss <input type="checkbox"/> Unintentional <input type="checkbox"/> Intentional <input type="checkbox"/> No		
Signs / Symptoms Please indicate severity of signs that have been present for at least 3 weeks.		None	Mild	Moderate	Severe	Very severe
2.	Wound, sores or lump in mouth or throat?	0	1	2	3	4
3.	Blood in saliva or sputum?	0	1	2	3	4
4.	Ear pain on one or both sides?	0	1	2	3	4
5.	Palpable new lump in the neck?	0	1	2	3	4
6.	Hoarseness?	0	1	2	3	4
7.	Pain or burning sensation in mouth or throat?	0	1	2	3	4
8.	Difficulty swallowing?	0	1	2	3	4
9.	Difficulty opening the mouth?	0	1	2	3	4
10.	Foul smelling breath?	0	1	2	3	4
11.	Chest pain?	0	1	2	3	4
12.	Shortness of breath?	0	1	2	3	4
13.	Cough?	0	1	2	3	4
14.	Noisy breathing?	0	1	2	3	4
15.	Fatigue or weakness?	0	1	2	3	4
16.	Loss of appetite?	0	1	2	3	4
17.	Persistent skin lesion (whole body)?	0	1	2	3	4
18.	Fear of the cancer coming back? How would you describe your worst-case fear? 0. I have no fear of recurrence 1. I have a little fear, with occasional thoughts but they don't really bother me 2. I am sometimes having fearful thoughts but I can usually manage these 3. I get a lot of fears of recurrence and these can really preoccupy my thoughts 4. I am fearful all the time that my cancer might return and I struggle with this	0	1	2	3	4

Diagnostic work-up for PRO-triggered visits

For visits triggered by PRO alerts or self-referral, diagnostic work-up follows center standards to assess REC/SPM and/or adverse events. These visits are documented as concomitant care events.

Study procedures beyond scheduled FU visits

Pilot phase Participants will fill out a paper PRO form monthly. The study team will call monthly to collect PRO

data, offering up to three reminders and further training, if needed. They will advise earlier visits for suspected REC/SPM with the center arranging these within 2 weeks.

Main study (ePRO) Participants will use a monthly ePRO with alerts triggering faster visits for REC/SPM within 2 weeks for the experimental group. The control group will not receive such alerts.

Table 3 Study assessment schedule

Individualized de-intensified and conventional follow-up schedule																										
X: For both arms O: For conventional arm only	Before inclusion ^a	Year 1				Year 2				Year 3				Year 4			Year 5			Non-scheduled visit at anytime						
		Months after randomization (+/- 4 weeks) ^b																								
		0	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60								
Patient pre-screening	X																									
Oral (recruitment flyers) and written patient information (PISIC)	X																									
Participation questionnaire	X ^h																									
MRI or CT Head and Neck with contrast and CT covering chest to pelvis in T2 N0 / PET/CT or PET/MRI for ≥ T3 and/or N+	X ^d																									
Inclusion and exclusion criteria ^c	X	X																								
Obtain signed informed consent		X																								
Randomization		X																								
Patient tumor, treatment characteristics		X																								
Height measurement		X																								
Weight measurement		X	O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Physical exam with fiber-/rigid endoscopy		X ⁱ	O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Instruction and training of signs/symptoms for REC/SPM, use of paper-/web-based PRO questionnaire and self-referral (Baseline, later if needed)		X	O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Assessment of signs and symptoms using the patient-reported outcomes (PRO) questionnaire		X	O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Schedule compliance, number of visit rescheduling			O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Assessment of REC/SPM			O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Assessment self-referral/PRO alert-initiated visits, other cancer-/treatment-related visits/procedures																			X							
Tobacco/Alcohol consumption		X		X		X		X		X		X		X	X	X	X	X	X							
Assessment of specific treatment-related adverse events ^j (CTCAE), SAE and outcome (since therapy or last assessment) ^k		X	O	X	O	X	O	X	O	X	O	X	O	X	X	X	X	X	X							
Performance status assessment (ECOG)		X		X		X		X		X		X		X	X	X	X	X	X							
Health-related Quality of Life (EORTC QLQ-C30 and QLQ-H&N43)		X		X		X		X		X		X		X	X	X	X	X	X							
EQ-5D-5L		X				X				X				X		X		X	X							
Concomitant care questionnaire				X		X		X		X		X		X	X	X	X	X	X							
MRI or CT Head and Neck with contrast and chest CT with contrast ^l				O				O																		
Chest CT without contrast ^{e, i}												(O)			(O)		(O)									
Patient-reported outcomes questionnaire recording by the patient		X	Monthly for both arms																							
Investigation / Imaging / Pandendoscopy			In case of clinical suspicion of REC/SPM ^f																							
Pregnancy test for women with childbearing potential ^g		X	Before each CT																							

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Baseline: timepoint of patient enrollment and randomization at 6 months after treatment

^a

3 - 6 months after therapy

^b

In case of rescheduling by patient as soon as possible within 2 weeks

^c

Before inclusion, pre-screening of eligibility base on available clinical data per-routine, confirmation of all eligibility criteria after informed consent had been obtained.

^d

If PET/CT or PET/MRI not available for ≥ T3 and/or N+: MRI or CT Head and Neck with contrast and CT covering chest to pelvis

^e

Chest CT without contrast marked with (O) is planned in participants with smoking history only (active smoking and ≥20 pack-years, or smoking habits at least within the last 15 years before cancer diagnosis and ≥20 pack-years). Current active smoker or former smoker of less than 20 pack-years do not get regular chest CT.

^f

REC/SPM: recurrence/second primary malignancy. According to the participating centers' standards

^g

Urine or blood test according to the standard of the center

^h

Pilotphase only

ⁱ

Result maximum within 4 weeks before enrolment, ideally on the day of inclusion

^j

Assessment of the events according to appendix 3 of the protocol according to standard of each site.

^k

PROs assessment should be performed at each visit by the participant before the medical consultation with the physician (scheduled or non-scheduled), but without comparison to the PROs monitored by the patients themselves at home (just for assessment of the symptoms).

^l

Scheduled imaging can be performed up to 4 weeks before the scheduled visit.

Self-referral visits

Additionally, any participant can initiate non-scheduled visits, with centers obliged to accommodate within 2 weeks.

Procedure for suspected REC/SPM

When REC/SPM is suspected, centers will follow their protocols for diagnostic work-up, recording all steps in the eCRF.

Post-confirmation a tumor board will outline the treatment approach. FU deviating from the study will conform to center standards, continuing for 5 years or until death. Data on REC/SPM diagnosis, treatment, and participant health status, including last weight, tobacco/alcohol use and symptom scores, will be collected and tracked.

Procedure in case of death

The eCRF will record the date and cause of death, distinguishing if it is related to the primary cancer, SPM, treatment, or other causes.

Retention and patient involvement strategies

To promote adherence, participants will get a color-coded alarm flyer outlining FU plans and space for future appointments. The flyer serves as a reminder for post-treatment progress and alerts patients to REC/SPM signs, emphasizing the importance of FU compliance and symptom-driven self-referral with quick contact details provided.

Training for early detection

Education on recognizing REC/SPM and adverse effects is given to all. The study uses a monthly ePRO (initially paper-based) to monitor symptoms with automated alerts for the experimental group to schedule earlier visits for REC/SPM symptoms and ensure questionnaire completion and adherence.

Non-attendance and recall procedures

For unattended appointments, participants will be contacted up to three times before marking “discontinuation of FU scheme” in the eCRF, unless primary endpoint data are obtainable from the family physician. Unconfirmed survival at 5 years will be “Lost to FU”.

Discontinuation of FU

Discontinuation criteria Participants can leave the FU study for REC/SPM diagnosis, serious adverse event

(SAE), significant medical condition, pregnancy, non-compliance after three recalls or by own request.

Status post-discontinuation Participants leaving the FU scheme, who do not withdraw consent remain in the trial and should follow the centers’ standard FU protocol.

Statistical analysis

After a 1-year recruitment period, the primary objective assessment will proceed based on participant accrual. A patient motivation questionnaire will be used to optimize enrollment and refine the study design. Adherence will be monitored until the final participant completes the 12-month FU in the second year. Data from the internal pilot phase will inform potential adjustments to the main trial but will not be analyzed separately unless the trial does not advance.

The internal pilot phase sample size is informed by feasibility objectives, including recruitment rates, participant retention, and protocol adherence, which are critical for assessing the study’s viability. Drawing on internal data from the Department of Oto-Rhino-Laryngology, Head and Neck Surgery at Inselspital, Bern University Hospital, the anticipated participant pool aligns with real-world metrics, ensuring a practical recruitment target for the main trial. This sample size allows for robust evaluation of recruitment and adherence metrics without compromising statistical power for the primary endpoint, given that the main trial’s effect measure—5-year restricted mean survival time—has been calibrated based on historical data approximated by a Weibull distribution (shape parameter $a = 1.18$, scale parameter $b = 10.25$), supporting a 5-year RMST of 4.65 years.

While the pilot’s sample size primarily assesses feasibility metrics, it does not account for the interim analysis, designed as non-binding and thus not impacting type I or II error rates. However, feasibility insights from the pilot phase will guide potential adjustments, ensuring that the full study, expected to enroll 550 participants, meets its recruitment and data quality standards.

Data from the internal pilot phase will be analyzed descriptively to assess feasibility metrics, such as recruitment rates and adherence. The participation questionnaire data will undergo descriptive and qualitative analysis to inform potential adjustments to the main trial, particularly in enrollment strategy and patient information. However, endpoint data collected during the pilot will only contribute to the main trial analysis if the study proceeds.

In the main study, analysis sets are defined in line with estimands, including intention-to-treat and two per-protocol sets. The intention-to-treat set will consist of

all randomized participants, regardless of protocol violations, while the per-protocol sets will define adherence differently: (a) “while-on-treatment” excludes non-adherence due to medical reasons, and (b) “hypothetical” includes any non-adherence. Adherence will be calculated based on scheduled visits completed within ± 4 -week window, with classification occurring only before REC/SPM occurrence. The main study’s primary endpoint, 5-year restricted mean survival time (RMST), and secondary endpoints will be analyzed using mixed-effects and negative binomial models, with adjustments for competing events [51–55]. A cost and cost-utility analysis will be performed if the trial shows promising non-inferiority results. This analysis will compare the incremental cost-utility ratio of the deintensified versus standard FU, using quality-adjusted life years (QALYs) and standardized healthcare costs.

For detailed procedures and analysis methods, refer to the full protocol submitted as supplementary material (see Additional file 1: DeintensiF-Full Protocol).

Discussion

Routine FU protocols for HNSCC patients typically include ENT exams and imaging. While various international guidelines support these standard FU schedules, retrospective studies offer mixed evidence on their impact, suggesting that standard FU does not consistently improve oncological outcomes over symptom-driven self-referral [28–34]. While two studies suggest a survival benefit of routine FU over self-reported symptoms [26, 27]. Evidence generally shows, that patients detect REC sooner than physical exams. Silent REC remains rare with low detection rates in routine visits [30, 35–38].

HPV-driven HNSCC, expected to become more prevalent by 2030, may further reshape FU protocols, emphasizing the need for validated methods that respond to both REC detection and changing etiological patterns [42, 56–60]. Current evidence to support the oncological benefits of regular FU remains sparse, raising questions about the value of routine visits compared to a symptom-based approach that has shown high sensitivity and negative predictive value [61–65].

Imaging remains a crucial yet controversial component of FU for HNSCC, largely due to its implications for QoL and cost. While imaging can aid in detecting locoregional REC early, its utility in asymptomatic cases is limited by high rates of false positives, which often lead to unnecessary interventions and added anxiety [66–68]. PET/CT scans following CXRT have shown greater sensitivity for detecting REC but vary in clinical impact depending on the timing of detection and disease progression [69–76]. Trials like PET-NECK suggest that PET/CT-guided

surveillance may achieve similar survival rates to standard FU protocols, with fewer surgeries and improved cost-effectiveness [76–86]. Despite these benefits, imaging beyond 6 months post-treatment for asymptomatic patients in complete remission remains debatable, as similar survival outcomes have been observed regardless of the detection method used [87].

For many patients, the FU process poses logistical, psychological, and financial burdens, often diminishing QoL. Studies indicate that while some patients feel reassured by routine FU, others experience heightened anxiety and express a preference for a less intense FU schedule [88–93]. Balancing the need for patient-centered care with evidence-based FU strategies could mitigate unnecessary radiation exposure, reduce stress, and lower costs associated with high false-positive rates, ultimately supporting a de-escalated FU approach [49, 94]. Additionally, FU protocols for HNSCC span several years and impose a significant financial burden. Research highlights the substantial QoL reductions experienced by HNC patients up to 24 months post-treatment, with a clear need for long-term care strategies that address persistent impairments [95]. While intensive FU has not demonstrated cost-effectiveness in other cancers, HNC-specific economic analyses remain limited. Addressing these economic and QoL impacts through a prospective, multicenter study could provide valuable insights into an optimal balance for FU strategies [96].

Ongoing research, including trials like HETeCo and SURVEILL’ORL, is currently exploring the cost-effectiveness and survival impact of PET/CT, while PETNECK 2 evaluates patient-initiated FU for low-risk HNSCC patients [NCT03519048, NCT02262221, NIHR200861]. These studies highlight the potential of targeted FU for selected HNSCC patients, particularly for those with HPV-positive cancer, offering valuable data that could be used as a reference point for broader studies, such as the one proposed here.

The presented DeintensiF trial aims to generate high-quality data to benefit patients and healthcare providers by establishing evidence-based follow-up (FU) guidelines for head and neck cancer. It will compare medical and patient-initiated FU procedures, assessing their impact on outcomes. Additionally, data on quality of life, anxiety, depression, and fear of recurrence will be collected to understand the psychological effects. Efforts to improve cost-efficiency will also be explored, potentially reshaping global clinical practice for HNC FU.

With REC primarily driven by symptoms, electronic patient-reported outcomes (ePROs), present a promising method for real-time symptom tracking, showing survival benefits in other cancer types through improved early detection and outcomes [36, 44].

However, the effectiveness of routine exams for detecting REC or SPM is uncertain due to high false-negative rates, and physical exams alone often fail to capture early signs of REC. With no proven survival benefit from routine over symptom-driven FU in HNC, the DeIntensiF main trial will further investigate whether a deintensified FU approach can safely match the mortality outcomes of standard FU while preserving patients' QoL. Symptom-based consultations may provide outcomes similar to those of standard FU in detecting REC or SPM, thereby presenting a patient-adapted, cost-efficient alternative.

Ethical considerations underscore the need for a randomized trial to address the current lack of prospective data on HNC follow-up (FU). The DeIntensiF trial will compare FU schedules with and without imaging to evaluate their effects on survival, oncological outcomes, and recurrence detection. It will also assess the influence of patient-reported symptoms, demographics, tumor characteristics, QoL, and costs across two FU schemes. Findings aim to support evidence-based, personalized surveillance tailored to tumor specifics and patient needs. The pilot phase will explore feasibility in randomizing patients with complete remission to different FU schemes. Participation is voluntary, with the right to withdraw anytime; no vulnerable participants will be included. To minimize the dropouts in the main study on the grounds of electronic illiteracy, patients are given the possibility to opt for an offline paper version of the ePROs questionnaire. Those patients will be called by the responsible site mimicking the web-based tool. Health literacy (HLS-EU-Q16) [97] and e-health literacy (eHEALS) [98] will be assessed during randomization to control for effects in compliance and applying (subgroup analysis). In addition to assessing health and e-health literacy during randomization, these metrics will be incorporated into our statistical models to adjust for potential variations in compliance and outcomes between patients using paper-based versus electronic PROs, ensuring that mode-related biases are minimized.

Frequent physical and radiological exams are a major logistical, psychological and financial burden for vulnerable and older cancer patients. We therefore expect de-intensification of FU to be especially welcomed by this group of patients. The trial offers efficient FU protocols that reduce unnecessary visits and risks, addressing QoL aspects often overlooked by current guidelines. For medical staff, it will generate evidence to optimize post-treatment care and inform international standards. The healthcare system may benefit through clearer value assessments of FU procedures and cost-efficient de-intensified practices if shown non-inferior, reshaping HNC FU worldwide.

Data will be securely coded with access limited to authorized personnel. The pilot trial is registered on a public registry (<https://www.clinicaltrials.gov>). The main study will also be registered on the above mentioned registry and on a public website providing details and regular updates. An abbreviated protocol of the main study will be published in an open access journal. Interim safety analyses, if deemed impactful on the trial or FU guidelines, may be communicated early, unless halted for safety reasons, in which case the interim forms the final analysis. The main findings, based on the final analysis, will be published in a peer-reviewed open-access journal within a year of the database lock, with further analyses following the main publication. Investigators involved are members of relevant medical societies and guideline committees and will work to reflect results in national and international guidelines. Results from the pilot study and the main trial will be presented to both patients and professionals through diverse formats, including congresses and media, to ensure practical application and influence on global FU practices.

Abbreviations

CXRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DFS	Disease-free survival
ENT	Ear, nose, and throat
eCRF	Electronic Case Report Form
ePRO	Electronic Patient-Reported Outcomes
FU	Follow-up
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PET	Positron emission tomography
PRO	Patient-reported outcomes
QALY	Quality-adjusted life year
QoL	Quality of life
REC	Recurrence
RMST	Restricted mean survival time
secTrial®	A secure online system for patient registration and randomization
SPM	Second primary malignancies
TNM	Tumor, node, metastasis
UICC	Union for International Cancer Control

Supplementary Information

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Additional file 1. DeIntensiF-Full Protocol.

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Authors' contributions

All authors have contributed to the development of the study protocol and manuscript. RG, SM, and OE are leading the project. RG, SC, and ST are responsible for overall trial management. RG, SM, and OE are all grant holders. RG, SM, TS, GR, GM, SH, DS, and PB are responsible for data collection. RG, SM, and GR are participating site leaders. AL, SC, and ST are trial statisticians. AL and ST are leading on the development and implementation of the statistical analysis plan. RG, SC, and OE are leading on the project's public and patient involvement activities.

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Data availability

An anonymized trial dataset will be available after the completion of the study. This will be shared on request, at the discretion of the authors. The study is currently ongoing.

Declarations

Ethics approval and consent to participate

Ethical approval for this study (KEK-BE: 2022–0966) was granted by the regional ethics commissions of Bern, Zurich as well as Nord-west and Central Switzerland. Written consent is obtained from all participants.

Consent for publication

All authors consent to the publication of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

- Stenson KM. Epidemiology/risk factors for head and neck cancer. UpToDate. 2022.
- Bernier J, et al. Postop irradiation with/without chemotherapy for advanced head/neck cancer. *N Engl J Med*. 2004;350:1945–52.
- Cooper JS, et al. Postop concurrent radiochemotherapy for high-risk squamous-cell carcinoma head/neck. *N Engl J Med*. 2004;350:1937–44.
- Bourhis J, et al. Hyperfractionated/accelerated radiotherapy in head/neck cancer: meta-analysis. *Lancet*. 2006;368:843–54.
- Pignon JP, et al. Chemotherapy in head/neck cancer (MACH-NC): Update on 93 trials. *Rad Oncol*. 2009;92:4–14.
- Cooper JS, et al. Second malignancies in head/neck cancer patients. *Int J Radiat Oncol Biol Phys*. 1989;17:449–56.
- Gregoire V, et al. EHNS-ESMO-ESTRO Guidelines for squamous cell carcinoma head/neck. *Ann Oncol*. 2010;21:v184–6.
- Yamamoto E, et al. Site-specific second primary cancer in early-stage head/neck squamous cell carcinoma. *Cancer*. 2002;94:2007–14.
- Ang P, et al. HPV and survival in oropharyngeal cancer patients. *N Engl J Med*. 2010;363:24–35.
- H. Survival changes in head/neck cancers: late 20th/early 21st century. *Oncologist*. 2010;15:994–1001.
- Roman BR, et al. AHS guidelines: follow-up/surveillance of head/neck cancer survivors. *Head Neck*. 2016;38:168–74.
- Dignonnet A, et al. Post-therapeutic surveillance strategies in head/neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol*. 2013;270:1569–80.
- National Comprehensive Cancer Network (NCCN), 2021. NCCN Guidelines: Head and Neck Cancers, Version 3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
- Hermans R, et al. Follow-up CT for laryngeal/hypopharyngeal squamous cell carcinoma after RT. *Radiology*. 2000;214:683–7.
- Paniello RC, et al. Follow-up practices for head and neck cancer: a professional societies comparison. *Arch Otolaryngol Head Neck Surg*. 1999;125:309–13.
- UK Clinicians Consensus. Head and neck cancer management guidance. *Eur J Surg Oncol*. 2001;27 Suppl A:S1–17.
- Kaanders JH, Hordijk GJ. Dutch national guideline for larynx carcinoma care. *Radiother Oncol*. 2002;63:299–307.
- Lester SE, Wight RG. Routine surveillance regimen in post-treatment head and neck cancer patients. *Clin Otolaryngol*. 2009;34:546–51.
- AIRO. AIRO guidelines. 2016. Available from: http://www.radioterapiaitalia.it/content_169.phtml. Cited May 8.
- AIOM. AIOM guidelines. 2016. Available from: <http://www.aiom.it/professionisti/documenti-scientifici/linee-guida/1,413,1>. Cited May 8.
- Robard L, et al. SFORL guidelines for Rendu-Osler-Weber disease epistaxis management. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2017;134:37–41.
- SSORL. Swiss guidelines for head and neck carcinoma care. 2019.
- Machiels JP, et al. Squamous cell carcinoma diagnosis/treatment guidelines. *Ann Oncol*. 2020;31:1462–75.
- National Comprehensive Cancer Network (NCCN), 2022. NCCN Guidelines for Lung Cancer Screening, Version 1.2022. Available at: <https://www.nccn.org/view/journals/jnccn/20/7/article-p754.html>.
- National Comprehensive Cancer Network (NCCN), 2024. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers, Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
- De Visscher AV, Manni JJ. Long-term follow-up for larynx, pharynx, oral cavity squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*. 1994;120:934–9.
- Ritoe SC, et al. Follow-up impact on laryngeal cancer life expectancy/mortality. *Cancer*. 2007;109:239–47.
- Agrawal A, et al. Long-term survival factors in recurrent head/neck cancer. *Laryngoscope*. 2009;119:2135–40.
- Boysen M, et al. Follow-up value in head/neck squamous cell carcinoma treated patients. *Eur J Cancer*. 1992;28:426–30.
- Flynn CJ, et al. Periodic follow-up's value in locally advanced head/neck cancer. *Clin Oncol*. 2010;22:868–73.
- Imbimbo M, et al. Intensive clinical/radiologic follow-up in head/neck cancer patients. *Otolaryngol Head Neck Surg*. 2019;161:635–42.
- Kissun D, et al. Recurrent oral/oropharyngeal squamous cell carcinoma timing/presentation. *Br J Oral Maxillofac Surg*. 2006;44:371–6.
- Schwartz DL, et al. Head/neck squamous cell carcinoma surveillance post-radiotherapy. *Head Neck*. 2003;25:990–9.
- Francis DO, et al. Surveillance impact on laryngeal cancer survival post Medicare. *Laryngoscope*. 2009;119:2337–44.
- Boysen ME, et al. Self-reported symptoms for recurrent head/neck cancer monitoring. *Anticancer Res*. 2016;36:2849–54.
- Kothari P, et al. Follow-up in head/neck cancer patients: an analysis. *Eur Arch Otorhinolaryngol*. 2011;268:1191–200.
- Pagh A, et al. Routine follow-up's value post head/neck cancer treatment: DAHANCA survey. *Acta Oncol*. 2013;52:277–84.
- Ilmarinen T, et al. De-escalation of post-treatment surveillance in oropharyngeal cancer. *Head Neck*. 2018. <https://doi.org/10.1002/hed.25593>.
- Masroor F, et al. NCCN-recommended posttreatment surveillance association with HPV-associated oropharyngeal squamous cell carcinoma outcomes. *JAMA Otolaryngol Head Neck Surg*. 2019;145:903–8.

40. Jung YH, et al. Regular follow-up policy's efficacy post head/neck cancer treatment. *Head & Neck*. 2018;40(4):E1–8. <https://doi.org/10.1002/hed.25267>.
41. Agrawal A, de Silva BW, Buckley BM, Schuller DE. Role of the physician versus the patient in the detection of recurrent disease following treatment for head and neck cancer. *Laryngoscope*. 2004;114:232–5.
42. Nisa L, La Macchia R, Boujelbene N, et al. Correlation between subjective evaluation of symptoms and objective findings in early recurrent head and neck squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg*. 2013;139:687–93.
43. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol*. 2016;34:557–65.
44. Denis F, Basch E, Septans AL, et al. Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. *JAMA*. 2019;321:306–7.
45. Roman BR, Goldenberg D, Givi B, Education Committee of American Head and Neck Society (AHNS). AHNS Series—Do you know your guidelines? Guideline recommended follow-up and surveillance of head and neck cancer survivors. *Head Neck*. 2016;38:168–74.
46. International Council for Harmonisation (ICH). ICH Harmonised Guideline – Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016. Available at: <https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline>.
47. Lin Y, Zhu M, Su Z. The pursuit of balance: an overview of covariate-adaptive randomization techniques in clinical trials. *Contemp Clin Trials*. 2015;45(Pt A):21–5.
48. Lauzon SD, et al. Statistical properties of minimal sufficient balance and minimization as methods for controlling. *Statistical Methods in Medical Research*. 2018;27(6):1831–44. <https://doi.org/10.1177/0962280217691792>.
49. Rogers SN, et al. A single-item screening question for fear of recurrence in head and neck cancer. *Eur Arch Otorhinolaryngol*. 2016;273(5):1235–42.
50. ECOG/WHO Performance Scale Group. ECOG Performance Status. 1982. Available at: https://en.wikipedia.org/wiki/Performance_status.
51. Mozumder SI, Rutherford MJ, Lambert PC. Estimating restricted mean survival time and expected life-years lost in the presence of competing risks within flexible parametric survival models. *BMC Med Res Methodol*. 2021;21:52. <https://doi.org/10.1186/s12874-021-01213-0>.
52. Fayers P, Bottomley A, EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC- the EORTC QLQ-C30. European organisation for research and treatment of cancer. *Eur J Cancer*. 2002;38(Suppl 4):S125–33.
53. Singer S, Amdal CD, Hammerlid E, et al. EORTC Quality of Life and the EORTC Head and Neck Cancer Groups. Available at: <https://www.eortc.org/>.
54. Singer S, et al. International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV. *Head & Neck*. 2019;41(6):1725–37. <https://doi.org/10.1002/hed.25609>.
55. Shakespeare TP, GebSKI VJ, Veness MJ, et al. Improving interpretation of clinical studies by use of confidence levels, clinical significance curves, and risk-benefit contours. *Lancet*. 2001;357:1349–53.
56. Chan KC, Hung EC, Woo JK, et al. Early detection of nasopharyngeal carcinoma by plasma Epstein-Barr virus DNA analysis in a surveillance program. *Cancer*. 2013;119:1838–44.
57. Hanna GJ, Supplee JG, Kuang Y, et al. Plasma HPV cell-free DNA monitoring in advanced HPV-associated oropharyngeal cancer. *Ann Oncol*. 2018;29:1980–6.
58. Szturcz P, Van Laer C, Simon C, et al. Follow-up of head and neck cancer survivors: tipping the balance of intensity. *Front Oncol*. 2020;6(10):688. <https://doi.org/10.3389/fonc.2020.00688>. eCollection 2020.
59. Lee DH, Roh JL, Baek S, et al. Second cancer incidence, risk factor, and specific mortality in head and neck squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 2013;149:579–86.
60. Jain KS, Sikora AG, Baxi SS, Morris LG. Synchronous cancers in patients with head and neck cancer: risks in the era of human papillomavirus-associated oropharyngeal cancer. *Cancer*. 2013;119:1832–7.
61. Malik A, et al. Outcomes of a telephone-based questionnaire for follow-up of patients who have completed curative-intent treatment for oral cancers. *JAMA Otolaryngol Head Neck Surg*. 2020;146(12):1102–8.
62. Kim AJ, Suh JD, Sercarz JA, et al. Salvage surgery with free flap reconstruction: factors affecting outcome after treatment of recurrent head and neck squamous carcinoma. *Laryngoscope*. 2007;117:1019–23.
63. Tan HK, Giger R, Auperin A, et al. Salvage surgery after concomitant chemoradiation in head and neck squamous cell carcinomas - stratification for postsalvage survival. *Head Neck*. 2010;32:139–47.
64. Zafereo ME, Hanasono MM, Rosenthal DJ, et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer*. 2009;115:5723–33.
65. Sullivan BP, Parks KA, Dean NR, et al. Utility of CT surveillance for primary site re-currence of squamous cell carcinoma of the head and neck. *Head Neck*. 2011;33:1547–50.
66. Hermans R. Posttreatment imaging in head and neck cancer. *Eur J Radiol*. 2008;66:501–11.
67. Kangelaris GT, Yom SS, Huang K, Wang SJ. Limited utility of routine surveillance MRI following chemoradiation for advanced-stage oropharynx carcinoma. *Int J Otolaryngol*. 2010;2010:904297. <https://doi.org/10.1155/2010/904297>.
68. Al-Shwaiheen FA, Wang SJ, Uzelac A, Yom SS, Ryan WR. The advantages and drawbacks of routine magnetic resonance imaging for long-term post-treatment locoregional surveillance of oral cavity squamous cell carcinoma. *Am J Otolaryngol*. 2015;36(3):415–23. <https://doi.org/10.1016/j.amjoto.2015.01.024>. Epub 2015 Feb 3.
69. Hemmat SM, et al. The limitations of routine magnetic resonance imaging for long-term post-treatment locoregional surveillance of salivary carcinoma. *ORL J Otorhinolaryngol Relat Spec*. 2015;77(3):132–40 PMID: 25697087.
70. Kao J, Vu HL, Genden EM, et al. The diagnostic and prognostic utility of positron emission tomography/computed tomography-based follow-up after radiotherapy for head and neck cancer. *Cancer*. 2009;115:4586–94.
71. Krabbe CA, Pruim J, Dijkstra PU, et al. 18F-FDG PET as a routine post-treatment surveillance tool in oral and oropharyngeal squamous cell carcinoma: a prospective study. *J Nucl Med*. 2009;50:1940–7.
72. Manikantan K, Dwivedi RC, Sayed SI, et al. Current concepts of surveillance and its significance in head and neck cancer. *Ann R Coll Surg Engl*. 2011;93(576–82):64.
73. Wang SJ. Surveillance radiologic imaging after treatment of oropharyngeal cancer: a review. *World J Surg Oncol*. 2015; 13: 94.
74. Ho AS, Tsao GJ, Chen FW, et al. Impact of positron emission tomography/computed tomography surveillance at 12 and 24 months for detecting head and neck cancer recurrence. *Cancer*. 2013;119:1349–56.
75. Dunsky KA, Wehrmann DJ, Osman MM, et al. PET-CT and the detection of the asymptomatic recurrence or second primary lesions in the treated head and neck cancer patient. *Laryngoscope*. 2013;123:2161–4.
76. Mehanna H, Wong WL, McConkey CC, PET-NECK Trial Management Group, et al. PET-CT surveillance versus neck dissection in advanced head and neck cancer. *N Engl J Med*. 2016;14(374):1444–54.
77. Corpman DW, Masroor F, Carpenter DM, et al. Posttreatment surveillance PET/CT for HPV-associated oropharyngeal cancer. *Head Neck*. 2019;41:456–62.
78. Anzai Y, Chang CP, Rowe K, Snyder J, Deshmukh V, Newman M, Fraser A, Smith K, Date A, Galvao C, Monroe M, Hashibe M. Surveillance imaging with PET/CT and CT and/or MRI for head and neck cancer and mortality: a population-based study. *Radiology*. 2023;307(2):e212915. <https://doi.org/10.1148/radiol.212915>. Epub 2023 Jan 10. PMID: 36625743; PMCID: PMC10102644.
79. Leclère JC, Clément C, Le Pennec R, Maheo C, Gujral DM, Schick U, Le Gal G, Marianowski R, Salaun PY, Abgral R. An intensive 18F-fluorodeoxyglucose-positron emission tomography with computed tomography-based strategy of follow-up in patients treated for head and neck squamous cell carcinoma who are clinically asymptomatic. *JAMA Netw Open*. 2023;6(8):e2326654. <https://doi.org/10.1001/jamanetworkopen.2023.26654>. PMID:37526935;PMCID:PMC10394574.
80. Warner GC, Cox GJ. Evaluation of chest radiography versus chest computed tomography in screening for pulmonary malignancy in advanced head and neck cancer. *J Otolaryngol*. 2003;32:107–9.

81. Hsu Y-B, Chu P-Y, Liu J-C, et al. Role of chest computed tomography in head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2008;134:1050–4.
82. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.
83. Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med*. 2013;368:1980–91.
84. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial (NELSON trial). *Randomized Controlled Trial N Engl J Med*. 2020;382:503–13.
85. Cheung MK, Ong SY, Goyal U, et al. False positive positron emission tomography / computed tomography scans in treated head and neck cancers. *Cureus*. 2017;9:e1146. <https://doi.org/10.7759/cureus.1146>.
86. Pagedar NA, Jayawardena A, Charlton ME, Hoffman HT. Second primary lung cancer after head and neck cancer: implications for screening computed tomography. *Ann Otol Rhinol Laryngol*. 2015;124(765–9):29.
87. Imbimbo M, Alfieri S, Botta L, et al. Surveillance of patients with head and neck cancer with an intensive clinical and radiologic follow-up. *Otolaryngol Head Neck Surg*. 2019;161:635–42.
88. Ghazali N, Cadwallader E, Lowe D, et al. Fear of recurrence among head and neck cancer survivors: longitudinal trends. *Psychooncol*. 2013;22:807–13.
89. Ghazali N, Roe B, Lowe D, et al. Uncovering patients' concerns in routine head and neck oncology follow up clinics: an exploratory study. *Br J Oral Maxillofac Surg*. 2013;51:294–300.
90. Koch L, Jansen L, Brenner H, Arndt V. Fear of recurrence and disease progression in long-term (≥5 years) cancer survivors—a systematic review of quantitative studies. *Psychooncol*. 2013;22:1–11.
91. Lampic C, Wennberg A, Schill JE, et al. Anxiety and cancer-related worry of cancer patients at routine follow-up visits. *Acta Oncol*. 1994;33:119–25.
92. Handschel J, Naujoks C, Kübler NR, Krüskemper G. Fear of recurrence significantly influences quality of life in oral cancer patients. *Oral Oncol*. 2012;48:1276–80.
93. Kanatas A, Ghazali N, Lowe D, et al. Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites. *Eur Arch Otorhinolaryngol*. 2013;270:1067–74.
94. Rogers SN, Scott B, Lowe D, et al. Fear of recurrence following head and neck cancer in the outpatient clinic. *Eur Arch Otorhinolaryngol*. 2010;267:1943–9.
95. Mueller SA, Riggauer J, Elicin O, et al. Patients' preferences concerning follow-up after curative head and neck cancer treatment: a cross-sectional pilot study. *Head Neck*. 2019;41:2174–81.
96. van Agthoven M, van Ineveld BM, de Boer MF, Leemans CR, Kneeg PP, Snow GB, Uyl-de Groot CA. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. *Eur J Cancer*. 2001;37(17):2204–11. [https://doi.org/10.1016/s0959-8049\(01\)00292-1](https://doi.org/10.1016/s0959-8049(01)00292-1). PMID: 11677108.
97. Pelikan J. Measuring comprehensive health literacy in general populations. HARC: Bethesda /Maryland; 2014.
98. Norman CD, Skinner HA. eHEALS: the ehealth literacy scale. *J Med Internet Res*. 2006;8:e27.
99. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group and-omized trials. *Trials*. 2010;11:32 PMID: 20334632.
100. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158:200–7.
101. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.

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