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Study Protocol
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Quitting smoking after head and neck squamous cell carcinoma diagnosis: a prospective study protocol

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Abstract

Quitting smoking after a diagnosis of squamous cell carcinoma of the head and neck (SCCHN) is associated with improved survival. However, the evidence supporting the systematic adoption of standardised counselling interventions is drawn primarily from limited retrospective data. To address this information gap, this prospective, multicentre study will assess whether standardised counselling increases the percentage of patients with long-term smoking cessation. The study will enrol adult patients with SCCHN who are active smokers or who quit within 30 days before diagnosis. Participants will receive counselling and will then be referred to dedicated smoking cessation centres. Follow-up assessments will be performed at regular intervals over three years and detect smoking status, adherence to cancer treatment, treatment-related toxicity, disease progression, survival outcomes (overall survival, progression-free survival, and cancer-specific survival), and quality of life. The primary outcome is the percentage of participants achieving sustained smoking cessation at 6 ± 1 months after enrolment. Targeted enrolment is 200 patients in 16 Italian centres, with enrolment planned to start in June 2025. Each recruiter will undergo specific training to ensure consistent delivery of counselling. The study results may guide clinical guidelines towards the integration of effective smoking cessation strategies into routine oncology practice.

Keywords: *head and neck cancer, smoking cessation, cancer survival, study protocol, squamous cell carcinoma*

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1. Introduction

Head and neck cancers, mostly in the form of squamous cell carcinoma (SCCHN), represent the seventh malignant neoplasm in the world, with an estimated ≈700,000 new cases per year, of which about 10,000 are in Italy [1]. SCCHN includes tumours with various localisations (e.g., oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx), classically associated with smoking exposure and alcohol intake [2]. Overall, tobacco smoking, abuse of alcohol, and human papillomavirus (HPV) infection represent the major risk factors for the development of SCCHN [2, 3]. Head and neck cancer incidence rates are increasing in Western Europe and the United States, mainly due to HPV-related oropharyngeal cancers [4]. In developing countries, tobacco use remains the principal determinant of SCCHN cases [5]. The five-year overall survival (OS) and disease-specific survival of patients with SCCHN are 46% and 63%, respectively, and over the past decades, a slow improvement in survival has been observed owing to advances in multidisciplinary care [6].

Quitting smoking after a cancer diagnosis has been associated with improved survival [7, 8]. Studies that have attempted to quantify the impact of post-diagnosis smoking cessation on the prognosis of patients with SCCHN are still limited in number, and some clinically relevant questions remain open, for example, possible interactions with disease stage and treatment modality. A recent meta-analysis by Caini and colleagues, based on 16 studies, estimated that smoking cessation can result in a 20% gain in overall survival (OS) compared with patients who are continued smokers; however, prospective data in this setting remain limited and inconclusive [9]. Warren and colleagues observed an improvement in OS among patients with SCCHN who quit smoking at diagnosis, but only in males; Sandoval and colleagues detected no positive impact of post-diagnosis smoking cessation on any survival endpoint [10–12]. Finally, a recent prospective study by Cinciripini and colleagues demonstrated that starting smoking-cessation treatment within six months of a cancer diagnosis can significantly increase survival, highlighting the importance of timely intervention in the management of smoking cancer patients [13].

Although evidence is still rather limited, there is almost unanimous agreement that quitting smoking improves prognosis. Considering the slow therapeutic progress made in recent decades, it is essential to test practical methods to help patients quit smoking. Several evidence-based strategies have been evaluated in oncology settings, including brief clinician advice; structured behavioural counselling delivered in person or by telephone; and pharmacolo-

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gical support such as nicotine replacement therapy, varenicline, or bupropion, often implemented through dedicated smoking-cessation services integrated into cancer care [14–18]. Randomised trials and systematic reviews in oncology, including in patients with head and neck cancer, suggest that multicomponent programmes combining behavioural counselling with pharmacotherapy and, when feasible, referral to tobacco-treatment specialists can increase quit attempts and short- to medium-term abstinence, although the available evidence remains heterogeneous [14, 15, 19]. Consistent with our choice of assessing smoking cessation at 6 ± 1 months, previous prospective data indicate that, when patients with SCCHN do quit, cessation most often occurs within the first six months after diagnosis [20]. Therefore, our main objective is to evaluate the effect of standardised counselling for post-diagnosis smoking cessation among patients with SCCHN.

1.1. Objectives

The primary objective of our study is to assess the effectiveness of a standardised, routine-practice counselling strategy for promoting post-diagnosis smoking cessation in patients with SCCHN. Effectiveness will be measured as the proportion of patients who are sustained quitters (see below) 6 ± 1 months following registration, i.e., from the initiation of the anti-smoking advice. Our secondary objectives are to estimate the association of smoking cessation after diagnosis with treatment adherence (radiation therapy [RT] or chemo-radiation [CRT]), in the context of treatment break, acute toxicity, treatment response, and survival metrics such as progression-free survival (PFS), cancer-specific survival (CSS), and OS; and quantify the impact of smoking cessation after diagnosis on quality of life (QoL).

2. Materials and methods

This study is observational, not-for-profit, longitudinal, prospective and nationwide multicentre-based, and is registered on ClinicalTrials.gov as NCTNCT06995417. This study protocol was developed in line with the SPIRIT guidelines, with adaptations appropriate for an observational prospective study. It aims to evaluate the effectiveness of a standardised clinical counselling strategy to promote smoking cessation after diagnosis among patients with SCCHN. Smoking cessation counselling is an established, non-experimental clinical practice and is recommended in national clinical practice guidelines [21, 22] and in international guidelines [23]. The leading centre is the Careggi University Hospital of Florence; the invitation to participate was sent to several Italian centres involved in the management of these patients. All patients with SCCHN who are candidates for curative-intent treatment and meet the inclusion criteria may be enrolled. Recruitment and data collection will take place in the outpatient clinics of the participating hospital centres that treat SCCHN, for example, radiotherapy, medical oncology, otorhinolaryngology and maxillofacial surgery. Sixteen Italian centres specialising in head and neck cancer will take part in recruitment (see "List of Participating Centres"). Considering the number of centres, the incidence of SCCHN, the prevalence of cigarette smoking in this population, and the number of patients that must be screened to obtain the desired sample size, the planned enrolment period is 24 months.

The study is endorsed by the North-Western Italy Oncology Group (Gruppo Oncologico del Nord-Ovest, GONO), a collaborative network of oncology centres and specialists, which promoted the study during the feasibility phase through its network.

2.1. Enrolment procedure

Once informed consent to participate in the study has been obtained, detailed information will be collected for each patient (see below).

At enrolment, the investigator will initiate a standardised strategy as part of routine practice: the investigator will carry out brief counselling ("minimal advice") using a questionnaire (Supplementary material S1) that, in addition to questions on current and past smoking habits, includes the Fagerström test (Supplementary material S2), a six-question tool used to assess physical nicotine dependence, and the adaptation of the Mondor test to assess the intention to quit smoking (Supplementary material S3) [24].

By incorporating these two tests into routine oncology consultations, clinicians can quantify nicotine dependence, assess motivation, and provide the first counselling. This approach empowers non-expert clinicians to recognise the prognostic importance of smoking cessation in cancer treatment, to initiate tailored advice on quitting and refer smokers to specialist cessation centres.

Patients wishing to stop smoking or considering quitting will also be informed about how to obtain support for quitting, with an explanation of the different options available locally. Every patient included in the study will be informed of the benefits of smoking cessation on survival and QoL. The investigator's counselling will aim to involve the patient and any family members, helping them understand the importance of adopting a proactive attitude toward smoking cessation. The patient will be referred to a specialist for standardised counselling at the reference smoking-cessation centre closest to the oncology treatment site, consistent with the current clinical practice.

Researchers running the study, especially those actively engaged in patient enrolment, will receive specific training before enrolment begins from staff of the smoking-cessation centre at the leading centre, Careggi University Hospital (also available via distance learning), to ensure that brief counselling is delivered in a standardised way across all participating centres. An enrolment period of 24 months with competitive enrolment is planned.

2.2. Follow-up

The follow-up visits will take place 3, 6, 12, 18, 24, 30, and 36 months after enrolment and will be held at the outpatient clinics of the participating centres. At every visit, the investigators will record clinical data and administer the smoking-specific and QoL questionnaires (**Table 1**).

Table 1 • Assessment schedule.

Assessments	Enrolment (M0)	Follow-up visit 1 (M3)	Follow-up visit 2 (M6)	Follow-up visit 3 (M12)	Follow-up visit 4 (M18)	Follow-up visit 5 (M24)	Follow-up visit 6 (M30)	Follow-up visit 7 (M36)
Informed consent	X							
Inclusion criteria check	X							
Exclusion criteria check	X							
Baseline data (demographics, tumour, patient's characteristics)	X							
Counselling activity and referral to the centre	X	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)
Smoking status evaluation	X	X	X	X	X	X	X	X
Fagerstrom's and Mondor's tests	X	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)	X (if still an active smoker)
QoL EORTC QLQ C30	X	X	X	X	X	X	X	X
QoL EORTC QLQ HN 43	X	X	X	X	X	X	X	X
Treatment and compliance	X	X	X	X	X	X	X	X
Disease progression evaluation	X	X	X	X	X	X	X	X

M0: Month 0; QoL EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; QoL EORTC QLQ HN 43: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Head and Neck Cancer Module (version 43).

2.3. Definition of study completion

The study will be complete once the three-year follow-up of every enrolled patient is completed. The planned study end date is June 2030.

2.4. Study population

The study population will consist of patients with SCCHN who are active smokers or have stopped smoking for less than 30 days at the time of the start of the programme (visits and instrumental examinations), leading to the cancer diagnosis, recruited from the 16 centres participating in the study.

It is expected that about 50 to 60% of patients with SCCHN will present with early-stage disease (stage I–II, TNM) and 50% with locally advanced disease (stage III–IV, TNM). These estimates are also usually related to the risk of recurrence, and the overall worse prognosis of locally advanced vs. early disease stage [25, 26].

2.4.1. Inclusion criteria

- Signed informed consent for study participation and the processing of personal data;
- Histologically confirmed SCCHN of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, or paranasal sinuses;
- Age > 18 years, with SCCHN at the above sites, and candidates for primary curative treatment with surgery, RT, or concomitant CRT, or induction chemotherapy followed by definitive RT or CRT;
- Patients with SCCHN who are active smokers or have stopped smoking within 30 days before the procedure leading to tumour diagnosis.

2.4.2. Exclusion criteria

- Patients with SCCHN who quit smoking more than 30 days before the diagnostic process;
- Exclusive use of electronic cigarettes at the start of cancer therapy;
- Patients with non-SCCHN tumours;
- Patients with recurrent/metastatic SCCHN who are deemed candidates for palliative management.

2.5. Study outcomes

2.5.1. Primary outcome

The primary outcome is the proportion of patients who achieve sustained smoking cessation ("sustained quitters", see below) at 6 $\pm$ 1 months after enrolment or after the start of smoking-cessation counselling.

2.5.2. Secondary outcomes

- For patients who received definitive or adjuvant RT or CRT: treatment adherence (expressed as days of therapy interruption) and acute toxicity according to CTCAE v5.0
- For every patient in the study: survival outcomes (tumour response, PFS, CSS, and OS) and QoL.

Oncological response will be recorded using the RECIST (Response Evaluation Criteria in Solid Tumours) criteria, classifying patients as responders (complete or partial response) or non-responders (stable or progressive disease).

Survival endpoints are local or distant progression (PFS) and death from head and neck cancer (HSC) or from any cause (OS).

Quality of life will be assessed with the validated questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC): QLQ-C30 (Supplementary material S4) and the QLQ-HN43 head and neck form (Supplementary materials S5).

2.6. Sample size

The observed quit rate will be compared with a benchmark from the literature: in the meta-analysis by Caini S. and colleagues, among studies on head-and-neck cancer, the proportion of patients who quit smoking at or after diagnosis ranged from about 24% to more than 70%, with a median of approximately 43% [18]. This median was used as the expected quit rate in the absence of dedicated counselling. For the sample-size calculation, we assumed that the counselling strategy would raise the quit rate by at least 10% above spontaneous cessation.

Recruiting 200 patients and assuming a 10% drop rate, the study will have >85% power to detect a statistically significant difference ($\alpha = 0.05$) between the reference rate of 43% and the 55% expected in this study, and will allow the percentage of smoking cessation to be estimated with an accuracy of less than 7% with a 95% confidence level. Therefore, the sample size chosen is adequate both for testing the hypothesis and for providing a reasonably accurate estimate of the smoking cessation rate.

2.7. Outcome assessment method

Smoking status will be assessed at the time of diagnosis and at 3, 6, 12, 18, 24, 30, and 36 months after the start of follow-up using dedicated questionnaires (see Schedule of Assessments—**Table 1**) covering smoking cessation and QoL.

- Active smoker: Patient reporting current cigarette use or having quit in the last 30 days.
- Quitter: Patient reports having stopped smoking more than 30 days earlier.

Participants who resume smoking after being classified as quitters will be reclassified as active smokers. Centres that routinely use objective measures of smoke exposure (for example, serum cotinine) may add these assessments to the self-reported data. In cases where a participant self-reports being a non-smoker but objective measures of smoke exposure are positive, the participant will be classified as an active smoker in the main analyses. Both self-reported smoking status and biomarker results will, nevertheless, be recorded in the database.

2.8. Data management

2.8.1. Data Collection

Key demographic, clinical, treatment, and follow-up information will be collected for each participant. The complete list of variables, including definitions and measurement details, is provided in Supplementary material S6.

2.8.2. Data pseudonymization

All study data will be pseudonymized and entered into an electronic case report form (eCRF).

- Each enrolled patient will receive a unique numeric code (Subject ID). The master key linking Subject ID to patient identity will be held securely by the principal investigator at each participating site.
- Source data will come from hospital information systems and, when necessary, from paper medical records.
- The eCRF database will be accessible only to study personnel. Each patient's records will be identified solely by their Subject ID.
- Subject IDs will be generated by the eCRF system. Only designated study staff and investigators will be able to link a Subject ID back to the patient's identity.
- Authorised personnel (as approved by the principal investigator) will have permission to enter, update, and analyse data.
- All data transfers between centres will use encrypted institutional or certified email accounts.

3. Statistical analysis plan

A descriptive analysis will be conducted for all variables, comparing the distribution of the variables collected (e.g., individual and tumour-related characteristics) between those who quit smoking and those who continued to smoke (with further subdivision between sustained quitters, intermittent quitters, and resumed smokers).

The main outcome will be calculated as the percentage of subjects, among those enrolled, who succeed in quitting smoking permanently (sustained quitters). Factors associated with smoking cessation will be investigated using multivariate logistic regression models. To assess the effect of the exposure factor (smoking cessation) on survival outcomes (OS, CSS, and PFS), the Kaplan–Meier method and the log-rank test will be used, and univariate and multivariate analyses will be conducted using the Cox proportional hazards model, modelling smoking status as a time-varying variable. Stratified analyses will be conducted for several variables of interest, particularly those related to disease severity (e.g., stage) and to the type of treatment administered. Multiple imputation methods will be used to treat missing data. An interim analysis of adherence and response to therapy and survival data (PFS) will be conducted 30 months after the start of the study.

The level of statistical significance is set at alpha = 0.05. Analyses will be conducted using the software Stata and R.

Given the length of the enrolment period, it is expected that the study will have a total duration of approximately five years from the start of enrolment (scheduled for June 2025).

3.1. Bias

The study findings may be affected by non-response bias (a type of selection bias), because patients who agree to participate could differ in important ways from those who decline. In addition, there is a potential risk of misclassification of smoking status due to socially desirable responding, that is, participants under-reporting or denying tobacco use.

4. Discussion

Smoking cessation counselling is not routinely incorporated into SCCHN care; when it is offered, two common features are missing: (a) organised training of physicians, and (b) an operational process for patients to access smoking cessation services. The latter is directly linked to our model, ensuring that every patient is introduced to a publicly funded cessation programme without additional infrastructure or extra costs. Our service model is sustainable and feasible: physicians must provide structured (and brief) standard smoking cessation counselling (a low time commitment intervention that is already suggested by international guidelines) [16, 17], and systematically refer patients to existing, staffed and funded cessation services. By leveraging existing resources, this model aims to be scalable, cost-neutral, and ready for immediate adoption in cancer care pathways.

Multiple meta-analyses, including diverse ranges of tumour types, indicate quitting at diagnosis (or close to diagnosis) is associated with an approximate 20% increase in overall survival; abstinence has a prognostic effect beyond SCCHN [9, 18].

Extensive retrospective research underscores the harm of continued smoking after an SCCHN diagnosis; cohort studies have shown that heavy smoking, defined by thresholds of approximately twenty-two pack-years, is associated with a more than 50% increase in mortality risk and significantly worse progression-free survival compared with lower exposures [27]. Matched analyses of patients undergoing radiotherapy have demonstrated that current smokers have markedly inferior five-year overall survival (about 23% vs. 55%), locoregional control (58% vs. 69%) and disease-free survival (42% vs. 65%) relative to patients who quit before treatment [28]. A recent meta-analysis of more than 6,000 patients found that continuing to smoke doubles the risk of mortality and locoregional failure [29]. In comparison, across several large observational cohorts, former smokers experience about a 30% reduction in overall mortality, with the greatest benefits accrued by former smokers who are abstinent for more than ten years [30].

In contrast, prospective evidence remains limited: in a longitudinal cohort of 835 patients with SCCHN, smoking cessation after diagnosis reduced mortality risk by approximately 60% compared with continued smoking, and conveyed a survival advantage even in intermittent quitters [31]. A single prospective study of smokers receiving multimodality therapy showed that almost half of patients with SCCHN continue smoking after treatment and that cessation, when it occurs, is most likely within the first six months after diagnosis [20]. These data show both the potential impact of cessation and the brief window for intervention. Comparable survival benefits have been documented outside the head-and-neck setting. For example, a prospective cohort of renal cell carcinoma patients demonstrated that smoking cessation after diagnosis substantially reduces the risk of all-cause mortality and disease progression [32].

As a result of accumulating evidence regarding survival benefit and cost-effectiveness, the incorporation of tobacco cessation into lung cancer clinical care pathways has been increasingly appreciated [33, 34]. In this regard, structured tobacco cessation will be dispersed, delayed, or absurdly absent; the disparity in cessation indicates no systematic tobacco pathway has been adapted for SCCHN, and that is exactly where our research study intends to fill this gap, by prospectively evaluating a low-grid referral-based tobacco cessation approach within the scope of routine care [35].

Moreover, the broad array of endpoints defined in our protocol, including treatment adherence, treatment toxicity, survival, and patient-reported QoL, may lend itself to clinical evaluation and a strong economic evaluation. Recent reviews suggest that tobacco-cessation programmes in cancer care almost always have a positive cost-effectiveness profile compared with many high-cost cancer treatments, and usually provide far more value of care for every quality-adjusted life-year achieved [36].

There is a network-wide role for health systems to optimise the tobacco treatment care trajectories in cancer care. For instance, the national “Just ASK” quality-improvement programme from the American College of Surgeons was recently reported to have accounted for the implementation of smoking status at 88% and subsequently at 92% accredited cancer centres [37], further suggesting that tobacco status assessment and referral can be introduced into clinical care pathways as part of a systematic national initiative. Notably, centres reported a variety of implementation strategies, such as education of providers, patient education materials, and electronic health records, to support smoking implementation in clinical workflows within the centre. Hence, these examples of adopting a multi-faceted approach in conjunction with other tobacco-cessation submissions show that smoking assessment and cessation referral should be part of cancer networks and their workflows [37].

Even modest absolute gains, if achieved at negligible marginal cost by exploiting existing human and structural resources, would strengthen the case for healthcare-system level adoption. If successful, this model may fill the implementation gap within routine SCCHN care and as a possible template for other cancers where tobacco cessation is not being optimally used despite clear evidence of need and benefit.

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Author contributions

Conceptualization, E.P., P.B., V.S., G.B., S.C. (Saverio Caini), C.C., M.D.R., S.C. (Salvatore Cardellicchio), and L.L.; methodology, E.P., P.B., V.S., S.C. (Saverio Caini), and M.D.R.; software, E.P., P.B., V.S., S.C. (Saverio Caini), and M.D.R.; validation, P.B., C.C., S.C. (Salvatore Cardellicchio), and L.L.; formal analysis, V.S., S.C. (Saverio Caini), and M.D.R.; investigation, E.P., P.B., V.S., G.B., S.C. (Saverio Caini), C.C., M.D.R., S.C. (Salvatore Cardellicchio), and L.L.; resources, P.B., C.C., S.C. (Salvatore Cardellicchio), and L.L.; data curation, E.P., V.S., S.C. (Saverio Caini), and M.D.R.; writing—original draft preparation, E.P., and M.D.R.; writing—review and editing, E.P., P.B., V.S., G.B., S.C. (Saverio Caini), C.C., M.D.R., S.C. (Salvatore Cardellicchio), and L.L.; visualisation, E.P., V.S., S.C. (Saverio Caini), and M.D.R.; supervision, P.B., S.C. (Saverio Caini), M.D.R., and L.L.; project administration, P.B., S.C. (Saverio Caini), M.D.R., and L.L. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Institutional review board statement

The protocol was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Regione Toscana—Area Vasta Centro (CEAVC) (protocol code 28400 approved on 2025 Apr 29).

Informed consent statement

Written informed consent for participation and for the publication of study-related data will be obtained from all participants prior to enrollment.

Supplementary materials

The supplementary materials are available at https://doi.org/10.20935/AcadOnco8080.

Additional information

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