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Prospective cohort assessing the determinants of radiation-induced skin complications in patients with head and neck cancer receiving preventive photobiomodulation

COH-PBM-3J: Prospective cohort assessing the determinants of radiation-induced skin complications in patients with head and neck cancer receiving preventive photobiomodulation

Version No. 2 of 15/09/2026

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1	23/06/2026	Initial version submitted to the CPP
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RESEARCH SUMMARY

Manager	Hôpital Forcilles-Fondation Cognacq-Jay
Person directing and supervising the research	Romain PLOUZE
Title	Prospective cohort assessing the determinants of radiation-induced skin complications in patients with head and neck cancer receiving preventive photobiomodulation
Acronym	COH-PBM-3J
Protocol version	No. 2 of 15/09/2026
Rationale / background	Head and neck cancers (HNC) are the 7th most common cancer worldwide. Radiotherapy, the mainstay of treatment, is accompanied by frequent and disabling skin complications (radiation dermatitis), affecting up to 95% of patients. Photobiomodulation (PBM) is recommended by MASCC 2023 [33,34] and WALT [59,61] for the prevention of radiation dermatitis in head and neck oncology. The DERMISHEAD study showed a 63% reduction in the incidence of grade ≥ 2 radiation dermatitis. However, a significant proportion of patients develop grade ≥ 2 radiation dermatitis despite this prevention (19-29% depending on the study). The determinants of this prevention failure remain poorly characterized, justifying a study focused on identifying predictive factors of response.
Primary Objective	To identify, in an exploratory manner, the clinical, demographic, tumor-related, treatment-related and functional factors potentially associated with the occurrence of grade ≥ 2 radiation dermatitis in patients with head and neck cancer treated with radiotherapy with preventive photobiomodulation (PBM).
Secondary objectives	1. To describe the dynamics of radiation dermatitis, in particular: - the frequency of severe forms (grade ≥ 3); - the time to onset; - the duration of evolution. 2. To describe the frequency of interruptions, adjustments or modifications of radiotherapy treatment attributable to radiation dermatitis, defined as any unplanned interruption lasting ≥ 5 consecutive days, any dose reduction ≥ 10% or any postponement of a session; 3. To describe the tolerability of photobiomodulation, including the nature, frequency and severity of adverse events potentially related to PBM; 4. To explore the association between functional, nutritional and pain status and the presence of radiation dermatitis; 5. To explore the association between quality of life and the presence of radiation dermatitis.
Research design	Prospective, single-center cohort study, interventional with minimal risks and constraints, falling under 2° of Article L.1121-1 of the French Public Health Code.
Inclusion criteria	Patients meeting all of the following criteria will be included in the study: 1. Age ≥ 18 years at the time of inclusion; 2. Diagnosis of head and neck cancer (histological, cytological or imaging confirmation), including the following sites: oral cavity, oropharynx, hypopharynx, larynx, nasopharynx,

	nasal cavity and paranasal sinuses. 3. Indication for curative-intent external beam radiotherapy (exclusive or adjuvant), with or without concomitant chemotherapy, exposing the cervical skin; 4. Possibility of starting preventive PBM from the start of radiotherapy according to the standardized protocol (3 sessions/week, 3 J/cm²); 5. Affiliation with a social security scheme or beneficiary of such a scheme, in accordance with current regulations; 6. Free, informed and express consent of the patient, obtained in writing after provision of an information sheet
Non-inclusion criteria	Patients presenting at least one of the following criteria will not be included in the study: 1. Inability to receive photobiomodulation (PBM), due to a contraindication or to patient refusal or to a radiotherapy duration of less than two weeks; 2. History of radiotherapy to the cervicofacial region. 3. Uncontrolled or active dermatological condition in the area to be irradiated, likely to interfere with the assessment of skin toxicities (psoriasis, eczema, cutaneous lupus, etc). 4. Ongoing photosensitizing treatment that cannot be interrupted or substituted during the radiotherapy period. 5. Severe immunosuppression, defined in particular by: HIV infection at the AIDS stage, long-term immunosuppressive treatment, history of organ transplantation. 6. Concomitant participation in another therapeutic trial likely to have an impact on the occurrence or severity of skin toxicities. 7. Person under a legal protection measure (guardianship, curatorship or court protection). 8. Pregnant or breastfeeding woman. 9. Patient refusal to participate in the study.
Primary endpoint	The primary endpoint is the occurrence of grade ≥ 2 radiation dermatitis, assessed according to the NCI-CTCAE v5.0 classification.
Secondary endpoints	1. To describe the dynamics of radiation dermatitis **Frequency of severe radiation dermatitis: proportion of patients presenting grade ≥ 3 radiation dermatitis (NCICTCAE v5.0.**- **Time to onset: time (in days) between the start of radiotherapy and the first grade ≥ 2 radiation dermatitis.** **Duration of evolution: duration (in days) between the date of the first radiation dermatitis ≥ 2 and the date of return to a grade < 2 (or disappearance of clinical signs as documented).** 2. To describe the frequency of interruptions/adjustments/modifications of radiotherapy attributable to radiation dermatitis **Unplanned interruption: proportion of patients who had an unplanned interruption of ≥ 5 consecutive days attributable to radiation dermatitis (yes/no).** **Dose reduction: proportion of patients who had a dose reduction ≥ 10% attributable to radiation dermatitis (yes/no).** **Session postponement: proportion of patients who had at least one session postponement attributable to radiation dermatitis (yes/no).** 3. To describe the tolerability of photobiomodulation (PBM)

	Incidence of adverse events (AEs) potentially related to PBM: proportion of patients who presented ≥ 1 AE attributable (or possibly attributable) to PBM (yes/no). **Nature of PBM-related AEs: descriptive typology of AEs (e.g. local discomfort, sensation of warmth, tingling, etc.), as collected during/after the session.** **Severity of PBM-related AEs: severity grading according to the NCI-CTCAE classification version 5.0 (Annex 1).** 4. To explore the association between functional/nutritional/pain status and the presence of radiation dermatitis **Functional status: handgrip value (handgrip strength) and sit-to-stand test value.** **Nutritional status: according to the HAS diagnostic criteria** **Pain status: VAS (0–10), use of opioids (yes/no)** Association endpoint: association between these statuses (functional, nutritional, pain) and the presence of radiation dermatitis, defined as grade ≥ 2 radiation dermatitis (NCICTCAE v5.0).- 5. To explore the association between quality of life and the presence of radiation dermatitis **EORTC QLQH&N35 questionnaire scores: total score, relevant subscores (dysphagia, mouth pain, xerostomia, mouth opening), collected at T2.-** Association endpoint: association between the scores and the presence of radiation dermatitis, defined as grade ≥ 2 radiation dermatitis.
Sample size	150 patients
Planned number of centers	1
Research duration	26 months
Statistical analyses of the data	The sample size is based on a feasibility approach using the events per variable rule (EPV ≥ 10). With an expected incidence of grade ≥ 2 radiation dermatitis of 23–30%, and taking into account 10% losses (135 analyzable patients), the inclusion of 150 patients will yield 31 to 40 events, i.e. a final multivariable model deliberately limited to 3 variables (EPV ≥ 10 rule). The main analysis will be based on logistic regression (univariate analyses: χ^2/Fisher tests and Student's t or Wilcoxon tests; selection $p<0.20$; parsimonious multivariable model). Secondary analyses will include: Cox models and Kaplan–Meier curves (time to onset), ordinal logistic regression (severity), logistic/Cox models with splines (dose–response relationship), χ^2/Fisher comparisons (adherence), models with interactions (subgroups), Wilcoxon tests and mixed models (quality of life), as well as multiple imputation in case of missing data.
Expected impact	This study aims to generate clinical knowledge to improve the prevention of radiation-induced skin toxicities in patients with head and neck cancers treated with radiotherapy with preventive photobiomodulation (PBM). It will make it possible to identify the factors associated with the occurrence of grade ≥ 2 radiation dermatitis despite a standardized protocol, and to better understand the inter-individual heterogeneity of response to PBM.

	From a professional standpoint, the results should make it possible to optimize and personalize PBM protocols, to structure practices within the department and to propose a reproducible model. The expected benefits include better tolerance of radiotherapy, a reduction in pain and nutritional complications, and a limitation of treatment interruptions.
Source of funding	Hôpital Forcilles-Fondation Cognacq-Jay
Independent Monitoring Committee planned	No

LIST OF ABBREVIATIONS

5STS	1-minute sit-to-stand test
AJCC	American Joint Committee on Cancer
AMPc	Cyclic adenosine monophosphate (cAMP)
ARC	Clinical research associate
ATP	Adenosine triphosphate
AUC	Area Under the Curve (area under the ROC curve)
Ca^{2+}	Intracellular calcium
CCO	Cytochrome c oxidase
CE	Conformité Européenne (European Conformity)
CIM-10	International Classification of Diseases, 10th revision (ICD-10)
CNIL	Commission Nationale de l'Informatique et des Libertés (French data protection authority)
COX-2	Cyclooxygenase 2
CPP	Comité de Protection des Personnes (Committee for the Protection of Persons, French ethics committee)
CTC	Head and neck cancer (HNC)
CTCAE	Common Terminology Criteria for Adverse Events
CW	Continuous Wave (continuous mode)
ECR	Randomized controlled trial (RCT)
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EVA	Visual Analog Scale (VAS)
FACT-H&N	Functional Assessment of Cancer Therapy – Head and Neck
Gy	Gray (radiotherapy dose unit)
HPV	Human Papillomavirus
HR	Hazard Ratio
IC	Confidence interval (CI)
IL	Interleukin
IMC	Body mass index (BMI)
IMRT	Intensity-Modulated Radiation Therapy
IR	Infrared
LLLT	Low-Level Laser Therapy
MAPK/ERK	Mitogen-Activated Protein Kinase / Extracellular signal-Regulated Kinase
MASCC	Multinational Association of Supportive Care in Cancer
MCID	Minimal Clinically Important Difference
MER	Radiation therapist (manipulateur en électroradiologie médicale)

MICE	Multiple Imputation by Chained Equations
MNAR	Missing Not At Random
MR	Reference methodology (Méthodologie de référence)
NCI	National Cancer Institute
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NRS-2002	Nutritional Risk Screening 2002
NSN	Required sample size
OMS	World Health Organization (WHO)
OR	Odds Ratio
ORL	Otorhinolaryngology (ENT / head and neck)
PBM	Photobiomodulation
PEG	Percutaneous endoscopic gastrostomy
PI3K/Akt	Phosphoinositide 3-kinase / Protein kinase B
PRO	Patient-Reported Outcome
PS OMS	WHO Performance Status
QLQ-H&N35	Quality of Life Questionnaire – Head and Neck 35 (EORTC)
RIPH	Research involving human participants (Recherche Impliquant la Personne Humaine)
ROC	Receiver Operating Characteristic
ROS	Reactive Oxygen Species
RT	Radiotherapy
SCMC	Collimated Monochromatic Semiconductor
SCPC	Collimated Polychromatic Semiconductor
SNG	Nasogastric tube
TNF-α	Tumor Necrosis Factor alpha
TNM	Tumor, Node, Metastasis (tumor classification)
UICC	Union for International Cancer Control
VIF	Variance Inflation Factor
VMAT	Volumetric Modulated Arc Therapy
WALT	World Association for Photobiomodulation Therapy
ΔΨm	Mitochondrial membrane potential

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1 Rationale for the research

1.1 Head and neck cancers

Head and neck cancers (HNC) comprise a heterogeneous group of malignant tumors affecting the upper aerodigestive tract: oral cavity, pharynx (nasopharynx, oropharynx, hypopharynx), larynx, nasal cavity, paranasal sinuses and salivary glands. They constitute a distinct nosological group according to the World Health Organization (WHO) classification (1,2).

The main risk factors identified include smoking, alcohol consumption, human papillomavirus infection (HPV, notably HPV-16), as well as occupational exposure to certain agents (asbestos, wood dust, nickel). The synergistic interaction between tobacco and alcohol considerably multiplies the risk of tumor development. The median age at diagnosis is around 60 years (2,3).

These cancers have a major functional impact on breathing (dyspnea, tracheotomy), phonation (dysphonia, aphonia) and swallowing (dysphagia, enteral nutrition). These impairments profoundly affect patients' quality of life (4,5).

The literature reports a suicide rate twice as high in patients with HNC compared with the general oncology population, reflecting the psychological distress associated with this disease (6).

1.2 Epidemiology of head and neck cancers

Head and neck cancers are the 7th most common cancer worldwide, with more than 1.1 million new cases diagnosed annually (7,8).

In France, the annual incidence is estimated at 15,000 new cases, resulting in approximately 3,600 deaths per year (9).

Five-year net survival data vary according to tumour location: 37% for cancers of the lips, oral cavity and pharynx, and 56% for cancers of the larynx (9). These figures underline the severity of the prognosis and the importance of optimal management, including the prevention of treatment-related complications.

1.3 Treatments for head and neck cancers

The treatment of head and neck cancers is based on a multidisciplinary approach combining, depending on the case, surgery, radiotherapy, chemotherapy, targeted therapies and immunotherapy. The choice of therapeutic strategy depends on tumour stage, location, the patient's general condition and their preferences (7).

Radiotherapy plays a central role in the therapeutic arsenal. It may be used alone (exclusive radiotherapy), in combination with chemotherapy (concurrent chemoradiotherapy), or in addition to surgery (adjuvant radiotherapy). Modern techniques (IMRT, VMAT) allow better sparing of healthy tissues (10,11).

The therapeutic challenge is to ensure oncological efficacy while preserving essential functions (phonation, breathing, swallowing) and minimising sequelae. Among the consequences of treatment, swallowing disorders are frequently reported, with a prevalence of 40-45% that can reach 80% after surgery (12,13).

1.4 Treatment complications

The treatment of head and neck cancers is accompanied by numerous acute and chronic complications, sometimes severe, which may compromise quality of life and treatment adherence (5,14).

1.4.1Skin complications

Acute radiation dermatitis is the most common cutaneous side effect of radiotherapy. Almost all patients develop some degree of skin reaction, ranging from mild erythema to moist desquamation in the most severe cases (15,16).

1.4.2 Functional and psychological complications

Dysphagia, dysphonia and trismus (mouth opening < 35 mm) are common sequelae (17). Approximately 75% of patients report significant changes in their appearance, and nearly 30% present major depressive symptoms (18,19).

The integration of Patient-Reported Outcomes (PROs) via validated questionnaires (EORTC QLQ-H&N35, FACT-H&N) makes it possible to objectify these impairments (18).

1.4.3 Radiation-induced skin complications

Radiation dermatitis (Skin erythema)

Skin erythema is a common inflammatory reaction observed in irradiated areas during radiotherapy treatment (15).

1.4.3.1 Mechanism of onset

The pathophysiology of acute radiation dermatitis is complex and depends in particular on damage to the proliferating basal cells of the epidermis. An initial phase of erythema occurs in connection with microvascular lesions inducing vasodilation and increased capillary permeability. This is followed by an inflammatory phase marked by the migration of immune cells to the irradiated area and by impaired tissue repair. The progressive destruction of basal keratinocytes compromises epidermal renewal, explaining the delayed onset of clinical signs and, in severe forms, moist desquamation and the risk of ulceration (19,20).

The differentiated keratinocytes of the stratum corneum are relatively radioresistant. In contrast, basal keratinocytes, which are responsible for epidermal cell renewal, are particularly radiosensitive. Exposure to ionising radiation causes damage to these basal cells, compromising the replacement of differentiated keratinocytes. This regenerative deficit explains the delayed clinical onset of skin symptoms (16,19). In cases of severe radiation dermatitis, an interruption of radiotherapy may be necessary, which may adversely affect treatment outcome and the patient's overall survival (20,21).

1.4.3.2 Classifications

Skin reactions generally become visible two to three weeks after the first radiotherapy session. Clinical assessment is based on standardised classification systems. The RTOG/EORTC scale, specific to radiotherapy, and the NCI-CTCAE v5.0, the international reference for clinical trials, allow severity to be graded (grades 0 to 4/5) (22,23).

NCI-CTCAE v5.0 classification – Radiation dermatitis

Grade	Description

1	Mild erythema, dry skin, dry desquamation
2	Moderate erythema, localised moist desquamation (skin folds), moderate pain
3	Extensive moist desquamation (outside skin folds), minor bleeding, severe pain
4	Severe ulceration, necrosis or bleeding requiring surgery
5	Death related to skin toxicity (exceptional)

1.4.3.3 Treatments and recommendations

To date, no preventive treatment has demonstrated robust efficacy (24). The MASCC 2023 guideline, established by a Delphi consensus involving 42 experts, recommends for prevention: photobiomodulation, protective films (Mepitel®, Hydrofilm®), topical corticosteroids (mometasone, betamethasone) and olive oil (25,26).

1.5 Photobiomodulation

1.5.1 Definition and general principles

Photobiomodulation (PBM), formerly referred to as low-level laser therapy (LLLT), is a non-invasive therapeutic modality based on the use of specific wavelengths of red light (620–700 nm) and near-infrared light (700–1100 nm). It is delivered using low-intensity lasers or light-emitting diodes (LEDs) (27,28).

1.5.2 Cellular and mitochondrial mechanisms of action

The biological effects of photobiomodulation are based on the interaction between light photons and specific intracellular chromophores. In accordance with the first law of photobiology, photons must be absorbed by a molecule (chromophore) to exert a biological effect. The pioneering work of Tiina Karu identified cytochrome C oxidase (CCO), the terminal enzyme of the mitochondrial respiratory chain (complex IV), as the main chromophore responsible for the beneficial effects of PBM (29,30).

1.5.3 Events at the mitochondrial level

Dissociation of nitric oxide (NO): NO inhibits CCO by binding to the oxygen binding site. Photon absorption induces photodissociation of NO, lifting this inhibition and allowing electron flow to resume (30,31).

Increased ATP production: restoration of electron flow increases oxidative phosphorylation and the production of adenosine triphosphate (29,32)

Modulation of the mitochondrial membrane potential (ΔΨm): transient hyperpolarisation influencing cell signalling (31).
Transient generation of reactive oxygen species (ROS): at low doses, ROS act as cytoprotective second messengers (31,33).

1.5.4 Retrograde signalling and nuclear effects

Mitochondrial events trigger retrograde signalling to the cytoplasm and nucleus: changes in intracellular calcium (Ca^{2+}), cAMP production, activation of the MAPK/ERK and PI3K/Akt pathways. At the nuclear level, the transcription factors NF-κB, AP-1 and HIF-1α are activated, modulating the expression of genes involved in inflammation, proliferation and cell survival (30,31,34).

1.5.4.1 Biphasic dose-response: the Arndt-Schulz law

A fundamental concept in PBM is the biphasic dose-response, described by the Arndt-Schulz law. This law states that weak stimuli accelerate biological activity, stronger stimuli increase it up to an optimal peak, and even stronger stimuli inhibit it. This biphasic response explains the crucial importance of technical parameters (35,36).

1.5.4.2 Resulting biological effects

Anti-inflammatory effect: reduction of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, COX-2) (31,37).
Pro-healing effect: stimulation of fibroblast and keratinocyte proliferation, collagen synthesis (27,38).
Analgesic effect: modulation of nociceptive transmission, release of endorphins (39)
Cytoprotective effect: protection of healthy cells against radiation-induced damage (40,41)

1.5.4.3 Oncological safety

Preclinical and clinical data are reassuring, as no stimulation of tumour growth has been observed at therapeutic doses. Tumour cells, characterised by anaerobic glycolytic metabolism (Warburg effect), indeed show a different response to PBM. Furthermore, the available systematic reviews have not shown any increase in the risk of recurrence (42,43).

1.5.5 Technical parameters and WALT recommendations

The efficacy of PBM depends closely on technical parameters. The World Association for Photobiomodulation Therapy (WALT) has published recommendations aimed at harmonising practices (44).

Fundamental PBM parameters

Parameter	Definition	Unit
Wavelength (λ)	Tissue penetration and target chromophore	nm
Irradiance	Power per unit area	mW/cm²
Fluence	Energy delivered per unit area	J/cm²
Emission mode	Continuous (CW) or pulsed	-

1.5.6 WALT recommendations for radiation dermatitis

In 2022, WALT published a position paper (expert consensus) on the use of PBM in the management of radiation-induced side effects (44,45). Regarding acute radiation dermatitis, the authors highlight the insufficiency of available data to formulate formal clinical recommendations. They nevertheless propose technical recommendations intended to guide clinical practice and research: use of an LED or laser device emitting in the visible or near-infrared range (400–1100 nm), at an irradiance of 10 to 150 mW/cm², for a target fluence of 1 Einstein (≈ 3 J/cm² at 810 nm), delivered within the 30 to 120 minutes preceding the radiotherapy session, 3 to 4 times per week for at least 5 to 6 weeks. In the event of inflammatory involvement of the subcutaneous tissues, a doubled fluence (2 Einstein) with a near-infrared device (730–800 nm) is suggested. The authors stress the need for methodologically rigorous multicentre trials to validate these parameters (46).

Parameter	Radiation dermatitis Preventive	Radiation dermatitis Therapeutic
Wavelength	400-1100 nm (visible or near-infrared)	730-800 nm (near-infrared)
Irradiance	10-150 mW/cm²	10-150 mW/cm²
Start of protocol	Day 1 (D1) of RT	As soon as lesions appear

Timing per session	30-120 before RT	Not specified (independent of RT)
Fluence per point	3 J/cm² (1 Einstein)	6 J/cm² (2 Einstein)
Frequency	3-4 sessions per week	3-4 sessions per week
Duration	Throughout radiotherapy	Until healing

1.5.7 Clinical efficacy of PBM in head and neck oncology

The DERMISHEAD study is the first multicentre, placebo-controlled randomised controlled trial, conducted in 46 patients with head and neck cancers. The results show that 28.6% of patients in the PBM group developed grade ≥ 2 radiation dermatitis, compared with 77.8% in the placebo group, i.e. a relative reduction of 63% (p = 0.001). A significant reduction in skin pain and an improvement in quality of life were also observed, with no adverse effects related to PBM (47).

The TRANSDERMIS study is a multicentre, double-blind randomised controlled trial conducted in 120 patients treated for breast cancer. The results show a significant reduction in the incidence of grade ≥ 2 radiation dermatitis as well as of moist desquamation (48).

The meta-analysis by Gobbo et al. (2023), including five studies, concludes that preventive PBM protects against the occurrence of severe radiation dermatitis and helps to limit treatment interruptions (45).

All available data allow the conclusion that: PBM is effective in the prevention of radiation dermatitis , PBM has a satisfactory safety profile, with no demonstrated risk of tumour stimulation, PBM is recommended by learned societies, notably the MASCC in its 2023 recommendations (25,26) and PBM contributes to improving quality of life as well as the continuity of oncological treatment (5,45,47).

1.5.8 Heterogeneity of response to photobiomodulation and rationale for the study

1.5.8.1 Clinical observation: incomplete preventive efficacy

PBM has demonstrated its efficacy in preventing radiotherapy-induced skin toxicities, notably radiation dermatitis. However, data from clinical trials highlight partial preventive efficacy, with moderate to severe complications persisting in a non-negligible proportion of patients.

Thus, in the DERMISHEAD study, although PBM achieved a 63% relative reduction in the incidence of grade ≥ 2 radiation dermatitis (28.6% vs 77.8%, p = 0.001), 19% of patients in the PBM group nevertheless developed grade 2 radiation dermatitis and 4% grade 3 radiation dermatitis (47).

1.5.8.2 Potential sources of response heterogeneity

The clinical efficacy of PBM appears to be influenced by several determinants, which can be grouped into patient-related, tumour- and treatment-related factors, as well as factors related to the PBM protocol itself.

1.5.9 Patient-related factors

Several individual characteristics are likely to modulate the biological response to PBM. Age is associated with a decrease in tissue regeneration capacity as well as impaired mitochondrial function. Skin phototype may also influence photon absorption and the depth of tissue penetration. Nutritional status is another determining factor, as malnutrition compromises repair and healing processes. Comorbidities, notably diabetes, vascular diseases and immunosuppression, may also modify the tissue response. Finally, toxic habits such as smoking and alcohol consumption contribute to vasoconstriction, tissue hypoxia and increased oxidative stress (45,47,49).

1.5.10 Factors related to the tumour and oncological treatments

The treatment burden and the nature of the treatments may also determine the occurrence of toxicities despite PBM. Tumour location and stage are determining factors. The total dose and the irradiation volume, notably in the case of unilateral or bilateral irradiation, also influence the risk of toxicity. Concurrent chemotherapy, known to potentiate radiation-induced effects, may increase these toxicities. Finally, prior surgery may contribute to tissue and vascular remodelling likely to modify treatment tolerance (10,11,47).

1.5.11 Factors related to the PBM protocol (35,36,50)

Finally, elements specific to the implementation of PBM may play a role:

- **Adherence to the protocol, including missed or incomplete sessions;**
- **Timing of sessions relative to radiotherapy fractions, which may influence the biological effect obtained.**

Although PBM is recommended by learned societies for the prevention of radiation dermatitis, via mechanisms involving mitochondrial stimulation and modulation of inflammation, a proportion of patients continue to develop grade ≥ 2 toxicities. This situation suggests the existence of variability in biological response and/or variability in the “effective PBM dose” delivered.

1.6 Research hypothesis

The efficacy of photobiomodulation in preventing radiation dermatitis is now established by good-quality evidence, justifying its inclusion in the MASCC 2023 international recommendations and its systematic implementation in our centre. However, a significant proportion of patients nevertheless develop complications despite this prevention.

We hypothesise that clinical, demographic, tumour-related, therapeutic and functional factors are associated with the occurrence of radiation-induced complications (grade ≥2 radiation dermatitis) in patients with head and neck cancer receiving radiotherapy with preventive photobiomodulation.

2 Objectives

Primary objective

To identify, in an exploratory manner, the clinical, demographic, tumour-related, therapeutic and functional factors potentially associated with the occurrence of grade ≥ 2 radiation dermatitis in patients with head and neck cancers treated with radiotherapy with preventive photobiomodulation.

The factors explored include:

- clinical and demographic factors: age, sex, skin phototype (Fitzpatrick classification), comorbidities, nutritional and functional status, smoking, alcoholism;
- tumour-related factors: location, TNM stage, histology;
- therapeutic factors: radiotherapy technique, total dose and dose per fraction, irradiated volumes, doses to organs at risk, concurrent chemotherapy;
- factors related to the PBM protocol: adherence, cumulative energy per anatomical site;

Secondary objectives

1. To describe the dynamics of radiation dermatitis, in particular:
   – the frequency of severe forms (grade ≥ 3);
   – the time to onset;
   – the duration of evolution.
2. To describe the frequency of interruptions, adaptations or modifications of radiotherapy treatment attributable to radiation dermatitis, defined as any unplanned interruption lasting ≥ 5 consecutive days, any dose reduction ≥ 10% or any postponement of a session;
3. To describe the tolerance of photobiomodulation, including the nature, frequency and severity of adverse events potentially related to PBM;
4. To explore the association between functional, nutritional and pain status and the presence of radiation dermatitis;
5. To explore the association between quality of life and the presence of radiation dermatitis.

3 Endpoints

Primary endpoint

The primary endpoint is the occurrence of grade ≥ 2 radiation dermatitis, assessed according to the NCI-CTCAE classification (appendix 1) version 5.0, corresponding in particular to moderate to confluent erythema, moist desquamation localised to skin folds and/or moderate oedema.

Secondary endpoint

1. To describe the dynamics of radiation dermatitis

Frequency of severe radiation dermatitis: proportion of patients with grade ≥ 3 radiation dermatitis (NCICTCAE v5.0.-

Time to onset: time (in days) between the start of radiotherapy and the first grade ≥ 2 radiation dermatitis.

Duration: time (in days) between the date of the first radiation dermatitis ≥ 2 and the date of return to grade < 2 (or resolution of clinical signs as documented).

2. To describe the frequency of radiotherapy interruptions/adaptations/modifications attributable to radiation dermatitis

Unplanned interruption: proportion of patients who had an unplanned interruption of ≥ 5 consecutive days attributable to radiation dermatitis (yes/no).

Dose reduction: proportion of patients who had a dose reduction of ≥ 10 % attributable to radiation dermatitis (yes/no).

Session postponement: proportion of patients who had at least one session postponed due to radiation dermatitis (yes/no).

3. To describe the tolerance of photobiomodulation (PBM)

Incidence of adverse events (AEs) (appendix 3) potentially related to PBM: proportion of patients who experienced ≥ 1 AE attributable (or possibly attributable) to PBM (yes/no).

Nature of PBM-related AEs: descriptive typology of AEs (e.g. local discomfort, sensation of warmth, tingling, etc.), as collected during/after the session.

Severity of PBM-related AEs: severity grading according to the NCI-CTCAE classification version 5.0 (Annex 1).

4. To explore the association between functional/nutritional/pain status and the presence of radiation dermatitis

Functional status: handgrip value (handgrip strength) and sit-to-stand test value.

Nutritional status: according to the HAS diagnostic criteria (appendix 4) (51).

Pain status: VAS (0–10), use of opioids (yes/no)

Association endpoint: association between these statuses (functional, nutritional, pain) and the presence of radiation dermatitis, defined as grade ≥ 2 radiation dermatitis (NCICTCAE v5.0).-

5. To explore the association between quality of life and the presence of radiation dermatitis

EORTC QLQH&N35 questionnaire scores: total score, relevant sub-scores (dysphagia, mouth pain, xerostomia, mouth opening), collected at T2.-

Association endpoint: association between the scores and the presence of radiation dermatitis, defined as grade ≥ 2 radiation dermatitis.

4 Eligibility criteria

Inclusion criteria

Patients meeting all of the following criteria will be included in the study:

1. Age ≥ 18 years at the time of inclusion;
2. Diagnosis of head and neck cancer (histological, cytological or imaging confirmation), including the following sites: oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, nasal cavity and paranasal sinuses.
3. Indication for curative-intent external beam radiotherapy (exclusive or adjuvant), with or without concomitant chemotherapy, exposing the cervical skin;
4. Ability to start preventive PBM from the beginning of radiotherapy according to the standardized protocol (3 sessions/week, 3 J/cm²);
5. Affiliation with a social security scheme or beneficiary of such a scheme, in accordance with the regulations in force;
6. Free, informed and express consent of the patient, obtained in writing after provision of an information sheet.

Non-inclusion criteria

Patients presenting at least one of the following criteria will not be included in the study:

1. Inability to receive photobiomodulation (PBM), due to a contraindication or to patient refusal or to a radiotherapy duration of less than two weeks;
2. History of radiotherapy to the cervicofacial region.
3. Uncontrolled or active dermatological condition in the area to be irradiated, likely to interfere with the assessment of skin toxicities (psoriasis, eczema, cutaneous lupus, etc).
4. Ongoing photosensitizing treatment that cannot be interrupted or substituted during the radiotherapy period.
5. Severe immunosuppression, defined in particular by: HIV infection at the AIDS stage, long-term immunosuppressive treatment, history of organ transplantation.
6. Concurrent participation in another therapeutic trial likely to have an impact on the occurrence or severity of skin toxicities.
7. Person subject to a legal protection measure (guardianship, curatorship or safeguard of justice).

8. Pregnant or breastfeeding woman.
9. Patient refusal to participate in the study.

Recruitment procedures

Patients will be recruited prospectively and consecutively within the radiotherapy department of Hôpital Forcilles, the sole inclusion centre.
One of the investigators will identify eligible patients and offer participation in the study.
Based on 2024 activity data, the department treats approximately 109 ENT / head and neck patients per year, i.e. a recruitment target of approximately 6-7 patients per month.

5 Research design

Type of study

This is a prospective, single-centre cohort study, interventional with minimal risks and constraints, falling under 2° of article L.1121-1 of the French Public Health Code.
The research will be conducted in accordance with the protocol.

Study location

The study will take place at Hôpital Forcilles, in the radiotherapy department.

Research scheme



Provisional research schedule

The recruitment period will be 24 months

- Submission to the CPP: July 2026
- Start of inclusions: September 2026
- Duration of the inclusion period: 24 months
- Duration of participation for each patient: approximately 7 weeks (corresponding to the duration of radiotherapy)
- End of inclusions: August 2028
- Total duration of the research: 26 months
- Communication at conferences: national and international scientific meetings in the fields of oncology and head and neck oncology, radiotherapy and swallowing or maxillofacial disorders;
- Publication: December 2028

6 Description of usual care in radiotherapy

Before the start of treatment, these patients receive a minimum of two consultations. The first is a paramedical consultation, performed by the radiation therapists (MER). The second is performed by the physician in charge of the treatment.

During the medical consultation, the physician performs a complete assessment of the patient's psychological, nutritional and functional status in order to screen for additional care needs. This assessment is based on the clinical evaluation and on the information collected by the MERs, who may administer various assessment questionnaires with the patient (quality of life, assessment of cognitive abilities, etc.). During these medical consultations, swallowing impairments and alterations of nutritional status are also screened for.

Throughout radiotherapy treatment, the patient has a weekly medical consultation with the physician in charge of their treatment. During this consultation, the onset of signs and symptoms indicating any of the adverse effects of the treatments is looked for (fatigue, loss of appetite, nausea, vomiting, digestive disorders).

Radiotherapy treatment generally comprises a total of 30 to 35 sessions, at a rate of five sessions per week (one session per day from Monday to Friday). They are delivered using the volumetric modulated arc therapy technique, lasting fifteen minutes. PMSI data allow us to estimate that approximately half of the patients treated with radiotherapy will also be treated concurrently with chemotherapy, most often at a rate of one session per week. These sessions take place in the Oncology Day Hospital of Hôpital Forcilles.

6.1 Preventive photobiomodulation

Preventive photobiomodulation is integrated into the standard care of patients with head and neck cancers treated with radiotherapy in our centre.

Sessions are performed using the ATP38® device (Swiss Bio Inov, Switzerland), a class IIa, CE-marked medical device (directive 93/42/EEC), which will be used in accordance with its instructions for use and the manufacturer's recommendations. The device uses collimated semiconductor technology and has an articulated panel composed of 3 flaps in the configuration used in our centre, allowing contactless irradiation of the cervicofacial skin areas. The emission spectrum covers wavelengths from 450 to 835 nm.

Protocol parameters

Parameter		**WALT 2022 recommendation**
Wavelength	800–835 nm (near IR)	400–1100 nm
Fluence per area	3 J/cm²	3 J/cm² (1 Einstein)

Frequency	3×/week (M-W-F)	3–4×/week
Timing	30–120 min before RT	30–120 min before RT
Total duration	Entire duration of RT	5–6 weeks
Distance	40 mm (contactless)	Not specified

Sessions begin from the first week of radiotherapy, at a rate of 3 sessions per week (ideally Monday-Wednesday-Friday), throughout the entire duration of treatment (6–7 weeks, i.e. 18–21 planned sessions). The treated areas correspond to the irradiation fields: cervical region (anterior and lateral), and submandibular region. The patient is placed in a supine or semi-seated position, with the flaps positioned at 40 mm without contact. Eye protection is mandatory for the patient and the operator.

Device-specific contraindications (pacemaker, epilepsy, pregnancy, prepubertal population) are checked at the pre-inclusion visit. The device undergoes preventive maintenance every 5 years in accordance with the manufacturer's recommendations.

Preventive PBM is implemented on medical prescription. Its practical application is carried out, depending on the department's organization, by the principal investigator (MER) or by registered nurses (IDE) who will have received formal training on the device, in accordance with the regulatory competencies of the MER (article R.4351-2 of the CSP) and of the IDE (article R.4311-2 of the CSP) (52).

6.2 Standardized data collection and traceability

For each session, the following elements will be documented on the individual PBM session traceability form (Appendix 6):

Technical parameters delivered:

- Date and time of the session
- Fluence delivered per area (J/cm²), irradiance (mW/cm²), application distance
- Exposure time, anatomical sites treated (skin)
- Energy delivered per session (J)

Protocol adherence:

- Session performed (yes/no)

In case of a missed session: documented reason (fatigue, logistical impossibility, pain, patient refusal, adverse event, other)

Time between the PBM session and the RT session

Adherence will be defined as the percentage of PBM sessions performed relative to the planned number (3 sessions/week × number of weeks of RT). It will be analysed as a continuous variable and in categories: optimal adherence (≥ 80 %) vs suboptimal (< 80 %).

6.3 Immediate tolerance of PBM:

Adverse events (AEs) potentially related to PBM will be collected at each session. The expected AEs are:

Expected AE	Estimated frequency	Usual severity
Local discomfort	Common (> 10 %)	Mild
Sensation of warmth	Common (> 10 %)	Mild
Tingling / paraesthesia	Uncommon (1–10 %)	Mild
Transient post-PBM erythema	Uncommon (1–10 %)	Mild
Local skin dryness	Rare (< 1 %)	Mild
Pruritus	Rare (< 1 %)	Mild

Sources: ATP38® manufacturer data, (44,47)

Clinical assessment of skin toxicities:

Radiation dermatitis will be assessed at each PBM session (3 times per week) according to the NCI-CTCAE v5.0 classification. The grade will be recorded on the traceability form.

6.4 Calculation of cumulative PBM energy via the TPS

For each included patient, the skin surface area within the irradiation field (in cm²) will be extracted from the treatment planning system (TPS Eclipse, Varian Medical Systems) interfaced with the ARIA information system.

Extraction method:

- The patient's external contour (“Patient External” structure) is generated automatically from the planning CT scan.
- The planning target volumes (PTV) are defined and the treatment plans are summed.
- The medical physicists calculate the projection of the PTV onto the Patient External surface, making it possible to determine the exposed skin surface area, expressed in cm².

This extraction is performed only once per patient, after validation of the treatment plan, and recorded in the research file.

Calculation of cumulative energy:

Cumulative energy (J) = Fluence (J/cm²) × Treated surface area (cm²) × Number of sessions performed

Cumulative energy will be calculated separately for the skin sites. This method, based on dosimetric data, ensures reproducible and operator-independent quantification. It will be used as the exposure variable in the dose-response analysis (secondary objective 2).

6.5 Associated supportive care

Local supportive care (protective films, topical corticosteroids, mouthwashes, local analgesics) is prescribed and adjusted according to the usual practices of the department.

Local co-interventions:

Protective films (Mepitel®, Hydrofilm®, etc.)

Topical corticosteroids

Sucralfate mouthwashes or gels

Local analgesics

Other topical treatments

Systematic documentation of co-interventions will make it possible to identify potential confounding factors and to describe the supportive care practices associated with PBM.

7 Assessment procedures added by the research

7.1 Functional assessment

The functional assessment will be performed in addition to the usual procedure. It consists of performing a sit-to-stand test and an assessment of handgrip strength.

- 1-minute sit-to-stand test: number of stands performed in 60 seconds. Measured at inclusion (T0) and at the end of treatment (T2).
- Handgrip (handgrip strength): measured using a hydraulic dynamometer. Measured at inclusion (T0) and at the end of treatment (T2).

These measurements will make it possible to explore the association between functional status and the occurrence of grade ≥ 2 radiation dermatitis.

7.2 Quality of life assessment (EORTC QLQ-H&N35)

The EORTC QLQ-H&N35 questionnaire will be used to assess the impact of radiation-induced toxicities on quality of life. It is the validated reference questionnaire in head and neck oncology [38], self-administered, comprising 35 items organized into 7 multi-item scales (pain, swallowing, senses, speech, social eating, social contact, sexuality) and 6 single items (teeth problems, mouth opening, dry mouth, sticky saliva, coughing, feeling ill).

Each item is scored from 1 (not at all) to 4 (very much). Scores are transformed into scales from 0 to 100, a high score indicating a high level of symptoms. The minimal clinically important difference (MCID) is estimated at 10 points for the symptom scales.

Administration schedule:

T0: at inclusion, before the start of radiotherapy (baseline)

T1: at mid-treatment (week 3 of radiotherapy)

T2: at the end of treatment (weeks 6–7 of radiotherapy)

The questionnaire will be given to the patient in paper format. The total score and the scores per dimension will be calculated according to the standard EORTC scoring manual.

7.3 Standardized photographic protocol

Clinical photographs of the irradiated areas will be taken in a standardized manner at inclusion, at W1, W3, W5 and at the end of treatment, under the following conditions: fixed distance of 30 cm, constant artificial lighting, neutral background, digital camera dedicated to the research. The images will be anonymized (identified by the inclusion code only) and stored in secure hosting. These photographs will serve as complementary documentation for the centralized review of radiation dermatitis grades in case of doubt about the reported grade. The patient's consent for taking and using the photographs is included in the general study consent form.

8 Conduct of the research

8.1 Pre-inclusion visit (D-16 +/- 3 days)

8.1.1 Verification of inclusion and non-inclusion criteria

During the initial medical consultation, one of the investigators verifies the presence of the inclusion criteria and the absence of the non-inclusion criteria in the medical file sent by the referring physician and in the patient's electronic record where applicable.

8.1.2 Patient information and consent

During this same consultation, and when all the criteria allowing the patient's inclusion are met, the investigator informs the patient of the purpose of the study. They provide the patient with all the information described in the information sheet (appendix 5) and, where applicable, obtain the patient's written, free, informed and express consent, obtained in writing after provision of an information sheet, in accordance with the consent form in the appendix.

8.2 Inclusion visit (D-11 +/- 3 days)

The inclusion visit takes place when the patient expresses their free and informed consent to participate in the study. It is performed by the principal investigator during the paramedical consultation, before or after the simulation CT scan. The principal investigator is responsible for collecting and transcribing the data into the research case report form.

During this visit, the following data will be collected:

8.1.2.1 1. Personal data

- Age, sex, height, weight, body mass index (BMI)
- Skin phototype according to the Fitzpatrick classification (I–VI)
- Smoking status: never / former / current, with quantification in pack-years
- Alcohol consumption: never / former / current

8.1.2.2 2. Medical history

- **ENT / head and neck or cervical surgery: yes/no; specify the nature if applicable**
- **Tracheostomy: yes/no; specify the date or duration if applicable**

- **Comorbidities: diabetes, arterial hypertension, vascular diseases, Charlson score**

8.1.2.3 3. Nutritional status

- Malnutrition: yes/no, with severity
- Oral feeding: total / partial / none
- If oral feeding is not complete: artificial feeding modalities (nasogastric tube, percutaneous gastrostomy)
- Assessment by NRS-2002 score, serum albumin, recent weight loss

8.1.2.4 4. Functional status

- 1-minute sit-to-stand test
- Handgrip (handgrip strength)

8.1.2.5 5. Head and neck cancer information

- Tumour site (ICD-10 code)
- TNM stage (AJCC/UICC 8th edition)
- Histological type
- HPV status (for oropharyngeal cancers)
- Chemotherapy performed or planned: number of sessions
- Surgery performed or planned: number of surgeries, operative report
- Time between diagnosis and start of radiotherapy

8.1.2.6 6. Radiotherapy information

- Extent of treatment
- Total prescribed dose (Gy)
- Dose per fraction and number of fractions
- Radiotherapy technique: IMRT, VMAT
- Irradiation volume: unilateral vs bilateral
- Exclusive or adjuvant radiotherapy
- Baseline assessment of skin condition (grade 0)
- Number of planned sessions

8.1.2.7 7. Photobiomodulation (PBM)

- First PBM session performed on the day of the first radiotherapy fraction (D0)

- Number of prescribed sessions

8.1.2.8 Additional questionnaires and assessments

- EORTC QLQ-H&N35 questionnaire (T0)
- Standardised photographs of the areas to be irradiated

8.3 Visits and follow-up during radiotherapy (W1-W7)

Systematic assessments (3 times per week, before each PBM session):

- Technical parameters: wavelength, fluence (J/cm²), irradiance (mW/cm²)
- Time between each radiotherapy session and the PBM session
- Reasons for missed sessions
- Radiation dermatitis grade (NCI-CTCAE v5.0)
- Traceability of the PBM session (parameters, duration, treated areas, time)

Weekly assessments:

- Standardised photographs (W1, W3, W5)
- Collection of adverse events

Intermediate assessment (W3 only):

- EORTC QLQ-H&N35 questionnaire (T1)

8.4 End-of-treatment visit

This visit will take place on the day of the last radiotherapy session.

During this visit, the following will be collected:

- Final assessment of skin toxicities (radiation dermatitis) according to the NCI-CTCAE v5.0 classification.
- Assessment of head and neck-specific quality of life, using the EORTC QLQ-H&N35 questionnaire (T2, final collection).
- Final clinical photographs of the irradiated skin areas, in accordance with the standardised procedures of the protocol.
- Assessment of adherence to photobiomodulation, including the total number of planned sessions, the number of sessions actually performed and the percentage of adherence to the protocol.

- Collection of modifications or interruptions of radiotherapy treatment, including duration, time of occurrence and causes, particularly when attributable to skin toxicities.
- Closure of the patient's participation in the study, with final transcription of the information into the research case report form.

Summary table

The table below summarises the assessments and procedures performed at each visit of the COH-PBM-3J protocol:

Assessment / Procedure	**Pre-inclusion (D-16 +/- 3 days)**	**Inclusion (D-11 +/- 3 days)**	**RT follow-up (W1-W7)**	**End of RT**
	Physician	**PI (MER)**	**PI (MER) or trained registered nurse**	**PI (MER) or trained registered nurse + Physician**
Consent and eligibility				
Patient information + provision of information leaflet	✓			
Collection of written consent	✓	✓		
Verification of eligibility criteria	✓			
Clinical and demographic data				
Tumour data (site, TNM, HPV)	✓			
RT treatment plan (dose, fractionation, volumes)	✓	Completes		

Concomitant chemotherapy (yes/no, agent)	✓	Completes		
Demographic data (age, sex, BMI, phototype)		✓		
Medical history and comorbidities		✓		
Active smoking (yes/no, pack-years)		✓		
Alcohol consumption		✓		
Clinical assessments				
Functional assessment (5STS or hand grip)		✓		✓
Nutritional assessment (weight, NRS-2002, serum albumin)		✓	✓	✓
Nutritional support (NGT, PEG)			✓	✓
Skin condition assessment — radiation dermatitis (CTCAE v5.0)		✓ (grade 0)	✓	✓
Pain (VAS 0-10)		✓	✓	✓
Quality of life questionnaires				
EORTC QLQ-H&N35		✓ (T0)	S3 (T1)	✓ (T2)
Photobiomodulation (PBM)				
PBM sessions (3×/week)			✓	✓
PBM traceability (session form)			✓	✓
PBM adherence assessment				✓
Documentation and follow-up				
Photographs of irradiated areas		✓	S1, S3, S5	✓
Co-interventions (supportive care)			✓	✓
Adverse events			✓	✓
Closure of participation				✓

Legend:

✓ = Procedure performed systematically

W1-W7 = Weekly assessment during the 7 weeks of radiotherapy

W3 = Assessment performed at week 3 only

T0 = inclusion (baseline); T1 = mid-treatment (W3); T2 = end of treatment (W6-W7)

PI = Principal investigator; MER = Radiation therapist (manipulateur en électroradiologie médicale)

"Completes" = The PI completes the data initiated by the physician from the medical record

Trained registered nurse = State-registered nurse (Infirmier diplômé d'État) who has received standardised training on the ATP38® device and the COH-PBM-3J protocol

9 Statistical aspects

9.1 Sample size calculation

9.1.1 Method — Events per variable (EPV) rule

As this is an exploratory cohort study aiming to identify factors associated with the occurrence of grade ≥ 2 radiation dermatitis using multivariable logistic regression, the sample size is based on a feasibility approach grounded in the events per variable rule (EPV ≥ 10), rather than on a power calculation for a single predefined effect.

The sample size of 150 patients is determined by the recruitment capacity of the department (109 ENT / head and neck patients/year, i.e. 6 to 7 inclusions/month over a 24-month period).

Taking into account an estimated loss to follow-up/missing data rate of 10%, the expected analysable sample size is 135 patients. Based on an expected incidence of grade ≥ 2 radiation dermatitis of 23 to 30% (DERMISHEAD (47)), the expected number of events is 31 to 41. According to the EPV ≥ 10 rule, this allows 3 to 4 variables to be included in the final multivariable model, after univariate selection ($p < 0.20$).

9.1.2 Expected statistical power

This approach is not based on a formal power calculation for a single hypothesis, as the approach is exploratory. For information, with 135 analysable patients and an expected incidence of 23 to 30%, the study would be able to detect, with 80% power (α = 5%), odds ratios of the order of 2.5 to 3 for a balanced binary exposure, an order of magnitude consistent with the effects reported in the literature on the determinants of radiation-induced skin toxicity.

9.2 Descriptive analysis

9.2.1 Description of the population at inclusion

All characteristics collected at inclusion will be described for the entire analysable population: clinical and demographic characteristics (age, sex, Fitzpatrick phototype, comorbidities, nutritional and functional status, smoking, alcohol use), tumour characteristics (site, TNM stage, histology), treatment characteristics (radiotherapy technique, total dose and dose per fraction, irradiated volumes, doses to organs at risk, concomitant chemotherapy) and characteristics related to the PBM protocol (adherence, cumulative energy per anatomical site).

A patient flow diagram (screened, included, followed up, withdrawn from the study) will be presented in accordance with the STROBE recommendations for cohort studies.

9.2.2 Methods of description

Quantitative variables will be described by mean and standard deviation if their distribution is compatible with normality (Shapiro-Wilk test, graphical inspection), or by median and interquartile range [Q1-Q3] otherwise. Qualitative variables will be described by counts and percentages, with 95% confidence intervals (Wilson method) for proportions of clinical interest (incidence of radiation dermatitis, tolerance of PBM). The number and percentage of missing data will be reported for each variable.

9.3 Analysis of the primary endpoint

9.3.1 Univariate analysis

Each candidate factor (clinical, demographic, tumour-related, treatment-related, related to the PBM protocol) will be compared between patients who developed grade ≥ 2 radiation dermatitis and those who did not. Quantitative variables will be compared using Student's t-test, or the Wilcoxon-Mann-Whitney test in case of non-normality, and

qualitative variables using the χ^2 test, or Fisher's exact test when expected counts are < 5. Factors associated in univariate analysis at a threshold of $p < 0.20$, as well as clinically relevant factors identified in the literature (age, total dose, concomitant chemotherapy), will be candidates for the multivariable analysis.

9.3.2 Multivariable analysis: logistic regression

A binary logistic regression model will be built to identify factors independently associated with the occurrence of grade ≥ 2 radiation dermatitis. In accordance with the EPV ≥ 10 rule (see 9.1.1), the final model will be deliberately limited to 3 variables, selected using a parsimonious selection procedure (Hosmer-Lemeshow purposeful selection approach) among the factors retained in the univariate analysis. Collinearity between variables will be checked (variance inflation factor, VIF < 5). Results will be expressed as adjusted odds ratios (aOR) with their 95% confidence intervals and the Wald test p-value. Model fit will be assessed using the Hosmer-Lemeshow test and its discriminative ability by the area under the ROC curve (AUC).

9.4 Secondary analyses

9.4.1 Analysis of time to onset of toxicities (survival analysis)

The time to occurrence of a first grade ≥ 2 radiation dermatitis, calculated from the start of radiotherapy, will be described using the Kaplan-Meier method (median time to occurrence with 95% CI), with patients who did not experience the event being censored at the end of follow-up. Curves will be compared between subgroups of interest (for example according to adherence to PBM) using the log-rank test. If the number of events allows, a univariate Cox model will explore the association between candidate factors and time to occurrence, in compliance with the EPV ≥ 10 rule.

9.4.2 Analysis of toxicity severity

The frequency of severe radiation dermatitis (grade ≥ 3) will be described with its 95% confidence interval (Wilson method). The association between candidate factors and the severity of radiation dermatitis (ordinal variable: grade < 2, grade 2, grade ≥ 3) will be explored using ordinal logistic regression (proportional odds model). The proportional odds assumption will be checked (Brant test); if it is not met, multinomial logistic regression will be used as an alternative.

9.4.3 PBM dose-response analysis

The relationship between the cumulative PBM energy delivered (or adherence to the protocol) and the risk of grade ≥ 2 radiation dermatitis will be explored using logistic regression, modelling dose as a continuous variable. The linearity of the relationship will be checked using restricted cubic splines; in case of a non-linear relationship, the dose-response curve will be presented graphically.

9.4.4 Per-protocol adherence analysis

A sensitivity analysis in the per-protocol population (patients who received ≥ 80% of the planned PBM sessions) will be performed in comparison with the intention-to-treat analysis. The reasons for missed or incomplete sessions will be described.

9.4.5 Subgroup analysis

Exploratory subgroup analyses (for example according to age, tumour site, concomitant chemotherapy) will be performed by introducing interaction terms into the logistic model. Given the limited power of these analyses, the results will be interpreted as hypothesis-generating and not as confirmatory.

9.4.6 Analysis of EORTC QLQ-H&N35 quality of life

The total score and relevant subscores of the EORTC QLQ-H&N35 questionnaire (dysphagia, mouth pain, xerostomia, mouth opening), collected at T2, will be compared between patients who developed grade ≥ 2 radiation dermatitis and the others, using Student's t-test or the Wilcoxon-Mann-Whitney test depending on the distribution. If several measurement time points are available, a linear mixed model (patient as random effect) will be used to account for the repeated structure of the data.

9.4.7 Additional descriptive analyses

The association between functional status (handgrip, sit-to-stand test), nutritional status (HAS criteria) and pain status (VAS, use of opioids) and the presence of grade ≥ 2 radiation dermatitis will be explored using the tests described in 9.3.1.

The frequency of unplanned interruptions, dose reductions and session postponements attributable to radiation dermatitis will be described (proportions with 95% CI).

The tolerance of PBM (incidence, nature and severity of adverse events potentially related to PBM) will be described in a purely descriptive manner.

9.4.8 Handling of missing data

In the event of missing data on the candidate covariates for the multivariable analysis (expected rate < 20%, mechanism assumed to be at random given the standardised prospective data collection), multiple imputation by chained equations (MICE, 20 imputations) will be performed, with a sensitivity analysis comparing the complete-case results with the results after imputation. The primary endpoint, collected during the weekly follow-up visits, is not expected to have significant missing data.

9.4.9 Additional statistical considerations

All statistical tests will be two-sided, with a significance level set at 5%. Analyses will be performed using R software (or SAS). No interim analysis is planned given the exploratory nature of the study. Given the number of secondary analyses, no formal adjustment for multiple comparisons is planned; results will be interpreted as exploratory and hypothesis-generating.

10 Expected results in terms of scientific and professional advances

This study aims to produce knowledge transferable to clinical practice regarding the prevention of radiation-induced skin toxicities in patients with head and neck cancer receiving preventive photobiomodulation (PBM).

Expected scientific advances

The study will make it possible:

- to identify the clinical, tumour-related, treatment-related and functional factors associated with the occurrence of grade ≥ 2 radiation dermatitis despite the implementation of a standardised preventive photobiomodulation protocol;
- to better characterise inter-individual heterogeneity in response to PBM, by highlighting profiles of patients at risk of non-response to this prevention strategy;
- to contribute to improving knowledge of the determinants of skin tolerance of cervicofacial radiotherapy treatments, in a context of integrated supportive care.

The expected results will add to scientific knowledge by focusing not on the overall efficacy of PBM, which has already been demonstrated, but on the determinants of its partial efficacy or failure in certain patients.

Expected professional advances

At the professional and organisational level, this study should make it possible:

- to optimise preventive photobiomodulation protocols, by adapting the technical parameters, schedule or intensity of care to the profiles of patients identified as being at high risk of complications;
- to promote a personalised approach to supportive care in radiotherapy, integrating risk stratification from the start of treatment;
- to structure and standardise photobiomodulation practices within the radiotherapy department, with a model reproducible in other centres;
- to showcase the team's expertise in the field of prevention of radiation-induced toxicities, through scientific communications and publications in peer-reviewed journals.

11 Expected benefits and risks for patients

11.1 Minimal risks and constraints added by the research

Participation in this research exposes patients only to minimal risks and constraints.

The photobiomodulation used in the study is already integrated into the standard care of patients treated with cervicofacial radiotherapy in our centre, in accordance with international recommendations. The potential risks associated with PBM are rare, benign and transient, and may include local discomfort, a sensation of warmth or tingling at the application site.

The additional burden related to the research is limited to the standardised collection of clinical data, the assessment of functional status through field tests, the completion of quality of life questionnaires and enhanced traceability of PBM sessions. No invasive examination or additional procedure compared with usual care is required.

At the doses used and according to current data in the literature, there is no evidence of an oncological risk or tumour stimulation related to photobiomodulation.

11.2 Expected benefits for the patient

The expected benefits for patients are both individual and collective.
At the individual level, participation in the study is part of a skin toxicity prevention strategy aimed at:

- Limiting the occurrence and severity of radiation dermatitis;
- Improving the overall tolerance of radiotherapy treatment;
- Reducing pain, functional impact and impairment of quality of life related to skin toxicities;
- Promoting the maintenance of oral feeding and limiting the need for invasive nutritional adaptations;
- Reducing the risk of interruptions or modifications of radiotherapy treatment attributable to toxicities.

At the collective level, the knowledge derived from this research will ultimately help improve the care of future patients, by enabling better identification of at-risk patients and more targeted adaptation of prevention strategies. This approach is part of a commitment to continuous improvement in the quality of care and the development of personalised supportive care in oncology.

12 Feasibility

Hôpital Forcilles has a radiotherapy department with a capacity exceeding 800 patients per year. Data on admissions for treatment of head and neck cancer over the last three years allow us to anticipate 150 patients over a 24-month period, taking into account:

- a more conservative estimate of incidence based on the local experience of our centre (30% of grade ≥ 2 complications despite PBM),
- an estimated attrition rate of 10% (lost to follow-up, missing data, study withdrawals).

Preventive photobiomodulation is performed on medical prescription, in accordance with the international MASCC/ISOO recommendations, but its practical application

relies on registered nurses. They are responsible for positioning the patient, the technical performance of the procedure, immediate clinical monitoring, assessment of tolerance and traceability of the sessions. These tasks fall within the regulatory framework of the prescribed nursing role, as defined by the French Public Health Code, including contributing to the implementation of treatments, clinical monitoring and evaluation of the effect of medical prescriptions (article R.4311 2 of the CSP).[63]

13 Ethical and regulatory aspects

Hôpital Forcilles-Fondation Cognacq-Jay, as sponsor, and the person(s) directing and supervising the research undertake that this research will be conducted in accordance with law no. 2004-806 of 9 August 2004 on public health policy and the regulatory provisions in force (articles L.1121-1, L.1121-2 and L.1121-3 of the French Public Health Code. The data recorded during this research will be processed electronically in compliance with law no. 78-17 of 6 January 1978 on information technology, data files and civil liberties, as amended by law no. 2018-493 of 20 June 2018 (decree no. 2018-687 of 1 August 2018) and ordinance no. 2018-1125 of 12 December 2018.
The research will be conducted in accordance with this protocol.

Role of the sponsor

The research committee of Hôpital Forcilles-Fondation Cognacq-Jay, sponsor of this research, submits the file for the opinion of the relevant CPP (Committee for the Protection of Persons) (CPP XXX), whose opinion will be notified in the information sheet intended for the persons concerned.
The natural or legal person who initiates this research, manages it and verifies that its funding is provided for is referred to as the sponsor.

Submission to the CPP

This research will be submitted to a Committee for the Protection of Persons that will be drawn by lot within the framework of the “Jardé law” (article L.1121-4 of the French Public Health Code, decree no. 2016-1537 of 16 November 2016, which came into force on 18 November 2016).

The opinion of the above-mentioned committee is notified in the information sheet intended for the persons concerned. A copy of this opinion and a summary of the research will be sent to the ANSM.

Data protection

This research is subject to law no. 78-17 of 6 January 1978 on information technology, data files and civil liberties, as amended by law no. 2018-493 of 20 June 2018 (decree no. 2018-687 of 1 August 2018). Information on the rights of persons participating in this research (right of access and rectification, right to object to the transmission of data covered by professional secrecy that may be used in the context of this research) is included in the information sheet intended for the patient.
A reference methodology specific to the processing of personal data carried out in the context of biomedical research as defined by law 2004-806 of 9 August 2004, since it falls within the scope of articles L.1121-1 et seq. of the French Public Health Code, was updated by the CNIL in May 2018 (deliberation no. 2018-153 of 3 May 2018) following the publication of European Regulation No. 2016/679 (General Data Protection Regulation). This methodology allows a simplified declaration procedure when the nature of the data collected in the research is compatible with the list provided by the CNIL in its reference document. This study falls under reference methodology MR001, with which Hôpital Forcilles-Fondation Cognacq-Jay has undertaken to comply.

Insurance

For the entire duration of the research, the Sponsor takes out insurance covering its own civil liability as well as that of any party involved in conducting the research, regardless of the nature of the links between the parties involved and the sponsor (article L.1121-10 of the French Public Health Code). It also provides compensation for the harmful consequences of the research for the person taking part in it and for their beneficiaries, unless it proves that the damage is not attributable to its fault or to that of any party involved, without the act of a third party or the voluntary withdrawal of the person who had initially consented to take part in the research being invoked against them. When the sponsor's liability is not engaged, victims may be compensated under the conditions provided for in article L.1142-3.

Hôpital Forcilles-Fondation Cognacq-Jay has taken out insurance under contract no. 163607 covering its civil liability as well as that of any party involved, with the company RELYENS, for the entire duration of the research, in accordance with article L.1121-10 of the French Public Health Code.

Substantial amendment to the protocol

The investigator or the coordinator informs the research committee of Hôpital Forcilles-Fondation Cognacq-Jay of any proposed amendment to the protocol. Any substantial amendment will be submitted by the sponsor of this research to the CPP for its opinion.

Information sheet and express consent

In accordance with article L.1122-1 of the French Public Health Code, the information given to persons taking part in the research is provided in a written document submitted beforehand to the Committee for the Protection of Persons. The ethical opinion of CPP Ouest III has been requested.

The site investigator offers the patient, or a relative if the patient is incapacitated, the opportunity to participate in the study. The investigator informs them orally of the study procedures and gives them the information sheet. If the patient agrees to participate in the protocol, their free, informed and express consent is obtained in writing using the consent form in the appendix. The form is signed in two copies; one copy is given to the patient, the other is kept by the investigator. The collection of consent is documented in the patient's medical record.

Where a relative of the patient has given consent, the patient will be informed of this research as soon as possible and their consent will be requested for the possible continuation of the research.

Patients are free to participate in the study or to withdraw from it at any time in accordance with article 21 of the GDPR. The data collected up to the patient's withdrawal of consent will be used unless the patient expressly requests otherwise. The patient's withdrawal of consent and their agreement or refusal regarding the use of previously collected data will be documented in the patient's medical record.

When this research is completed, the person taking part in the research may be informed of the overall results of this research according to the procedures that will be specified to them in the information document.

Planned timeline for publication of the results in an international journal

The planned timeline for publication of the results is 30 months.

Data management

For each subject, an identification code (corresponding to the centre number-inclusion number-Initial of Last Name Initial of First Name) will be assigned. The data collected will be confidential and coded (only the identification code will appear). The correspondence table linking the assigned identification code to the participant's name will be kept by the principal investigator in a file with electronically restricted access rights. The data will be entered into a password-protected Excel® file held by the principal investigator. Data processing and statistical analysis will be carried out on the premises of Hôpital Forcilles-Fondation Cognacq-Jay.

The sponsor owns the data and no use or transmission to a third party may be made without its prior agreement.

The specific documents of a Category 2 interventional research study (“Jardé law”, decree no. 2016-1537 of 16 November 2016, which came into force on 18 November 2016) involving minimal risks and constraints will be archived by all parties for a period of 15 years after the end of the research.

This indexed archive includes:

- the successive versions of the protocol (identified by version number and date);
- correspondence letters;
- the inclusion list or register;
- the data collection document;
- the appendices specific to the research;
- the final research report.

The database used for the statistical analysis must also be archived by the person responsible for the analysis (paper or electronic format).

Human and financial resources

Hôpital Forcilles-Fondation Cognacq-Jay has the human, material and technical resources to carry out this research project.

Data ownership

Hôpital Forcilles-Fondation Cognacq-Jay owns the data and no use or transmission to a third party may be made without its prior agreement.

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15 APPENDICES

15.1 Appendix 1: NCI-CTCAE classification

Grade	Description
1	Mild erythema, skin dryness, dry desquamation
2	Moderate erythema, localized moist desquamation (skin folds), moderate pain
3	Extensive moist desquamation (outside skin folds), minor bleeding, severe pain
4	Severe ulcerations, necrosis or bleeding requiring surgery
5	Death related to skin toxicity (exceptional)

15.2 Appendix 2: PBM adverse events

Expected AE	Estimated frequency	Usual severity
Local discomfort	Common (> 10 %)	Mild
Sensation of warmth	Common (> 10 %)	Mild
Tingling / paresthesia	Uncommon (1–10 %)	Mild
Transient post-PBM erythema	Uncommon (1–10 %)	Mild
Local skin dryness	Rare (< 1 %)	Mild
Pruritus	Rare (< 1 %)	Mild

15.3 Appendix 3: Nutritional status according to the HAS classification – Diagnosis of malnutrition in adults

HAS recommendations 2019 (adults < 70 years) & 2021 (≥ 70 years)

Diagnostic rule: the diagnosis is based on the combination of at least 1 phenotypic criterion AND at least 1 etiological criterion. The diagnosis is exclusively clinical.

Step 1 — Diagnostic criteria

Phenotypic criteria	• Weight loss ≥ 5 % in 1 month or ≥ 10 % in 6 months or ≥ 10 % / pre-illness weight • BMI < 18.5 kg/m² • Confirmed sarcopenia: – Grip strength < 27 kg (M) / < 16 kg (F) – Appendicular muscle mass < 20 kg (M) / < 15 kg (F)	• Weight loss ≥ 5 % in 1 month or ≥ 10 % in 6 months or ≥ 10 % / pre-illness weight • BMI < 22 kg/m² (higher threshold than before age 70) • Confirmed sarcopenia: (same thresholds as < 70 years)
Etiological criteria	**Identical for both age groups:** • Reduced food intake ≥ 50 % for > 1 week, or any reduction for > 2 weeks compared with requirements • Reduced absorption: maldigestion / malabsorption • Aggression state (hypercatabolism): acute disease, progressive chronic disease or progressive malignant disease	

Step 2 — Severity levels

Level	Adults < 70 years	Adults ≥ 70 years
Moderate malnutrition	• BMI between 17 and < 18.5 kg/m² or • Weight loss ≥ 5 % in 1 month or ≥ 10 % in 6 months or • Serum albumin between 30 and < 35 g/L	• BMI between 20 and < 22 kg/m² or • Weight loss ≥ 5 % in 1 month or ≥ 10 % in 6 months or • Serum albumin between 30 and < 35 g/L
Severe malnutrition	• BMI < 17 kg/m²	• BMI < 20 kg/m²

	or • Weight loss ≥ 10 % in 1 month or ≥ 15 % in 6 months or • Serum albumin < 30 g/L	or • Weight loss ≥ 10 % in 1 month or ≥ 15 % in 6 months or • Serum albumin < 30 g/L

Key points

• Serum albumin is NOT a diagnostic criterion — it is used only to assess severity.

• A normal or high BMI does not rule out malnutrition (an overweight person may be malnourished).

• If the etiological criterion disappears (e.g., resumption of food intake), the diagnosis of malnutrition persists as long as the phenotypic criterion is present.

• Weight must be measured at each consultation and/or hospitalization and recorded in the medical record.

15.4 Appendix 4: Patient information sheet and consent form

COH-PBM-3J

Prospective cohort evaluating the determinants of radiation-induced skin complications in patients with head and neck cancer receiving preventive photobiomodulation

ID RCB: 2026-A01480-51

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SPONSOR OF THE RESEARCH

Clinical Research Committee Hôpital Forcilles-Fondation Cognacq-Jay Route de Servon 77150 Férolles-Attilly
Telephone: 01.60.64.61.31
Fax: 01.60.02.15.09

Dear Madam, Dear Sir,

Doctor Michel GOZY, radiation oncologist, physician investigator in charge of the COH-PBM-3J research, practising in the Radiotherapy Department of Hôpital Forcilles – Fondation Cognacq-Jay (route de Servon, 77150 Férolles-Attilly), is inviting you to take part in this research. The invitation may also be made by Doctor Elena LIHIOUEL or Doctor Loïc HERMET, co-investigator physicians.

Your decision regarding this participation is entirely free and voluntary.

Please read the information below carefully, ask any questions you wish, and take the time you need to think it over before making your decision.

You have a minimum, non-reducible reflection period of 24 hours between the time you are given this information sheet and the possible signing of the consent form. The sheet is given to you during the pre-inclusion consultation; your consent can only be obtained at a subsequent consultation. Information and collection of consent are never carried out during the same consultation. This period may be extended at your request, with no consequence for your care.

Who is conducting this research?

Doctor Michel GOZY, radiation oncologist, is the physician investigator in charge of the research. He assumes medical responsibility: verification of your eligibility, information, collection of your consent, medical follow-up, and assessment and management of adverse events.

Doctors Elena LIHIOUEL (radiation oncologist) and Loïc HERMET (ENT specialist), co-investigator physicians, have the same medical obligations.

Mr Romain PLOUZE, coordinating investigator, is a radiation therapist and is not a physician. Under the medical responsibility of the physician investigators and within the scope of his regulatory competencies (article R.4351-2 of the French Public Health Code), he performs the photobiomodulation sessions, the functional assessments, the administration of the questionnaires and the data collection. He does not perform any medical function.

What is the purpose of this research?

The objective of this research is to identify the factors that influence the effectiveness of photobiomodulation (PBM) in preventing skin complications related to radiotherapy for head and neck cancers. PBM is a light-based treatment, painless and contactless, which is already used routinely in our department to reduce the side effects of radiotherapy on the skin. Although this technique is effective for most patients, some still develop complications. We wish to understand why, in order to best tailor the care of each patient.

How is this research conducted?

Your radiotherapy treatment will take place exactly as planned, without any modification. Like all patients treated with radiotherapy for an ENT cancer in our department, you will receive photobiomodulation (PBM) sessions 3 times a week throughout your radiotherapy. Each session lasts approximately 10 to 15 minutes and

consists of applying near-infrared light, without contact and without pain, to the irradiated areas (skin of the neck).

If you agree to take part, we will collect certain information about your treatment in more detail: the parameters of the PBM sessions, the progression of your skin, your pain and your diet. We will also ask you to complete a short quality-of-life questionnaire on three occasions: before the start of radiotherapy, at mid-treatment and at the end of treatment.

Standardized photographs of the irradiated areas will be taken during treatment to document the progression of your skin. Your face is not photographed, and these images, stored in coded form, do not allow you to be identified.

How is the quality-of-life questionnaire conducted?

The questionnaire used is the EORTC QLQ-H&N35 questionnaire (French version, 35 questions), validated for head and neck cancers. It is attached to this sheet in the form in which it will be given to you.

It is a paper self-administered questionnaire, which you complete yourself in a consultation room of the Radiotherapy Department, during consultations that are already scheduled: before the start of radiotherapy, at mid-treatment and at the end of treatment. An investigator remains available nearby to answer any question of understanding, without influencing the choice of your answers. If you are unable to complete it yourself, an investigator may read the questions to you and write down your answers without interpreting them. It takes approximately 10 minutes. You may choose not to answer one or more questions, without having to justify yourself and without any consequence for your care.

What will this research involve for you?

The constraints related to your participation are minimal. They consist of a more detailed collection of clinical data during your usual visits and the completion of a quality-of-life questionnaire. No additional examinations or invasive procedures are required compared with your usual care. The additional burden is estimated at approximately 20 minutes per week.

Possible adverse effects

Photobiomodulation is a non-invasive technique whose adverse effects are rare, benign and transient. They may include slight local discomfort, a sensation of warmth or tingling in the treated area. These effects disappear spontaneously within a few minutes. At the doses used and according to current data in the literature, there is no evidence of an oncological risk or of tumour stimulation related to photobiomodulation. Your participation in this research will not result in any additional costs.

What are the expected benefits of this research?

On an individual level, you will benefit from closer monitoring of the progression of your skin during radiotherapy, as well as preventive photobiomodulation in accordance with international recommendations. On a collective level, the results of this study will help to better identify patients at risk of complications despite PBM, in order to adapt prevention strategies and improve the care of future patients

What are the conditions for taking part in this study?

This research is restricted to adults aged 18 years or over. To take part in this research, you must be affiliated with or a beneficiary of a social security scheme. However, your participation in this research will not result in any additional costs for you compared with those incurred in your usual care.

Planned number of patients and duration of the research?

This research will last 26 months, with a recruitment period of 24 months in order to include 150 patients. Your participation will last approximately 2 months, corresponding to the duration of your radiotherapy.

What data are collected for the research?

The data collected in this research include: your demographic data (age, sex, weight, height), your skin phototype, your medical history and lifestyle habits (smoking, alcohol), your nutritional status, the characteristics of your cancer (location, stage) and of your treatment (radiotherapy, any chemotherapy), the parameters of and adherence to the photobiomodulation sessions, the assessment of the condition of your skin at each visit, your answers to the quality-of-life questionnaire, as well as standardized photographs of the irradiated areas. No information that could identify you will be

provided to anyone, except Doctor Michel GOZY, physician investigator in charge of the research, the co-investigator physicians (Doctors Elena LIHIOUEL and Loïc HERMET), the coordinating investigator (Mr Romain PLOUZE) and authorized members of the research team, all of whom are bound by professional secrecy. All data collected will be confidential and coded, then analysed within the clinical research unit of Hôpital Forcilles-Fondation Cognacq-Jay, sponsor of the research. The identification list (correspondence between your study code and your identity) will be kept strictly confidential.

In accordance with the regulations in force, the data will be kept until the final report of the research has been completed and then archived for 15 years.

The data controller is the sponsor, Hôpital Forcilles- Fondation Cognacq-Jay, route de Servon 77150 Férolles-Attilly.

Legal bases for data processing

Data processing is based on the legitimate interests of the data controller, article 6 paragraph 1 point f, read in conjunction with the necessity of processing for scientific research purposes, article 9 paragraph 2 point j, of European Regulation No. 2016/679 (General Data Protection Regulation, GDPR). It is also governed by French law no. 78-17 of 6 January 1978 on information technology, data files and civil liberties, amended in particular by law no. 2018-493 of 20 June 2018 on the protection of personal data.

What are your rights?

Your participation in this research is entirely free and voluntary. You have the right not to take part in this research.

You are free to take part in the study or to withdraw from it at any time, without having to give a reason. Doctor Michel GOZY, physician investigator in charge of the research, or one of the co-investigator physicians (Doctors Elena LIHIOUEL and Loïc HERMET), must provide you with all the necessary explanations regarding this research, which must comply with the provisions of Article 13 of European Regulation No. 2016/679 (General Data Protection Regulation, GDPR). In accordance with Article L.1122-1 of the French Public Health Code, the entire research file was submitted beforehand to the Committee for the Protection of Persons (CPP) Sud-Ouest et Outre-Mer IV, which issued a favourable opinion on ...../...../.....

Hôpital Forcilles-Fondation Cognacq-Jay has taken out insurance under contract No. 163607 with Relyens Mutual Insurance, covering its civil liability and that of any person involved.

You may stop your participation in the research at any time without giving a reason. This will have no consequence either on the quality of the care and treatments that will be

provided to you or on your relationship with the care team. The data collected up to the withdrawal of your consent will be used unless you expressly request otherwise. Indeed, in accordance with Article 17 of the GDPR, you have the right to request the erasure of the data concerning you that have already been collected. The withdrawal of your consent and your agreement or refusal to the use of your previously collected data will be recorded in your medical file.

You may exercise these rights, indifferently and without distinction, with the Data Protection Officer of Fondation Cognacq-Jay (dpo@cognacq-jay.fr, or by post: Hôpital Forcilles-Fondation Cognacq-Jay, Data Protection Officer, route de Servon 77150 Férolles-Attilly) or with the physician investigator in charge of the research. If you contact the investigator, he/she acts only as an intermediary and forwards your request to the sponsor's Data Protection Officer, who will respond to it.

In application of the provisions of Article L. 1111-7 of the French Public Health Code, you may also access all of the medical data concerning you, either directly or through a physician of your choice.

Your medical file will remain confidential and may only be consulted under the responsibility of the physician in charge of your treatment, as well as by the health authorities and by persons duly authorised by Hôpital Forcilles-Fondation Cognacq-Jay for the research and bound by professional secrecy.

In accordance with Article L.1122-1 of the French Public Health Code, you will be informed, at your request, of the overall results of this research once it has been completed.

If, after reading this information, discussing it with the investigator physician and observing the minimum, non-reducible reflection period of 24 hours, you decide to take part in this research, the information about the research and your written consent will be recorded and dated in your medical file.

Agreement to take part in this research is free and voluntary. You may refuse or withdraw your agreement at any time without having to give any explanation and without suffering any prejudice as a result.

Who to contact?

The following persons are available to provide you with any further information, before, during and after the research:

Doctor Michel GOZY, radiation oncologist, physician investigator in charge of the research – tel.: 01 60 64 61 52 – mgozy@cognacq-jay.fr
Doctor Elena LIHIOUEL, radiation oncologist, co-investigator – tel.: 01 60 64 63 09
Doctor Loïc HERMET, ENT physician, co-investigator – tel.: 01 60 64 60 37
Mr Romain PLOUZE, radiation therapist, coordinating investigator – tel.: 01 60 64 63 41 – rplouze@cognacq-jay.fr
Data Protection Officer of Fondation Cognacq-Jay – dpo@cognacq-jay.fr

15.4.1 Consent Form

I, the undersigned (surname, first name): .....
Date of birth: ...../...../.....
declare the following, each of the statements below having been brought distinctly to my attention:
1. Doctor Michel GOZY, radiation oncologist, physician investigator in charge of the research, practising in the Radiotherapy department of Hôpital Forcilles – Fondation Cognacq-Jay [or Doctor ....., co-investigator physician], has proposed that I take part in the research COH-PBM-3J – Prospective cohort evaluating the determinants of radiation-induced skin complications in patients with head and neck cancer receiving preventive photobiomodulation.
2. I have received, read and understood the information sheet version No. 2 of 15/09/2026, a copy of which has been given to me, as well as the quality of life questionnaire appended to it.
3. I have been informed of the objectives, procedure, duration, expected benefits, constraints and foreseeable risks of this research.
4. I have had the opportunity to ask all the questions I wished and have received appropriate answers.
5. I have had a minimum, non-reducible reflection period of 24 hours between receiving the information sheet and signing this form. The information and the collection of my consent did not take place during the same consultation.
6. I know that Doctor Michel GOZY, physician investigator in charge of the research, or one of the co-investigator physicians (Doctors Elena LIHIOUEL and Loïc HERMET),

will inform me at any time, during or after my participation, of any new information likely to change my willingness to take part.

7. I freely and voluntarily agree to take part in this research.

8. I am free to withdraw from the research at any time, without having to give a reason, without suffering any prejudice and without any consequence on the quality of the care provided to me or on my relationship with the care team.

9. I have been informed that the data already collected as of the date of my withdrawal may be used, unless I expressly request their erasure.

10. I agree that the health data concerning me, collected during this research, may be processed electronically in coded form by the sponsor, Hôpital Forcilles-Fondation Cognacq-Jay, which is the controller of this processing.

11. I agree that these data may be consulted, in compliance with professional secrecy, by persons duly authorised by the sponsor for the quality control of the research, as well as by the competent health authorities.

12. I agree that standardised photographs of the irradiated areas may be taken and stored in coded form, my face not being photographed.

13. I have been informed that this processing is carried out in accordance with Regulation (EU) 2016/679 (GDPR) and amended Law No. 78-17 of 6 January 1978, in particular by Law No. 2018-493 of 20 June 2018 on the protection of personal data.

14. I have been informed that I have the right of access, rectification, erasure, restriction and objection (Articles 15 to 21 of the GDPR). I may exercise these rights, indifferently and without distinction, with the Data Protection Officer of Fondation Cognacq-Jay (dpo@cognacq-jay.fr) or with the physician investigator in charge of the research. If I contact the investigator, he/she acts only as an intermediary and forwards my request to the sponsor's Data Protection Officer, who will respond to it.

15. I have been informed that I may lodge a complaint with the Commission Nationale de l’Informatique et des Libertés (CNIL, French data protection authority) (www.cnil.fr).

16. I have been informed that the Committee for the Protection of Persons (CPP) Sud-Ouest et Outre-Mer IV issued a favourable opinion on this research on ...../...../.....

17. I have been informed that the sponsor has taken out civil liability insurance with Relyens Mutual Insurance (policy No. 163607).

18. I confirm that I am an adult, aged 18 years or over.

19. I confirm that I am affiliated to a social security scheme or am a beneficiary of such a scheme.
20. I declare that I have answered all the questions asked about my medical history and agree to follow the instructions given to me by the care team.
21. I have been informed that I will be informed, at my request, of the overall results of this research (Article L.1122-1 of the French Public Health Code).
22. My consent does not release the sponsor or the investigators from their responsibilities. All my rights guaranteed by law are preserved. This form is drawn up in two original copies: one copy is given to me, the other is kept by the investigator.

The investigator,
Surname:
First name:
Position:
Date:

Signature:

The patient,
Surname:
First name:
Date:

Signature:

15.5 Appendix 5: Photobiomodulation compliance monitoring sheets

PATIENT IDENTIFICATION			
Inclusion No.:		Date:	
Initials:		RT week:	

PHOTOBIOMODULATION SESSION			
Session performed:	☐ Yes ☐ No	Session No.:	
Session date:		PBM start time:	
PBM end time:		RT start time:	
PBM → RT interval:		Compliant 30-120 min:	☐ Yes ☐ No
If session not performed — Reason:			
☐ Patient fatigue ☐ Patient refusal ☐ Logistical impossibility ☐ Pain ☐ PBM-related AE ☐ Other: _____			

TECHNICAL PARAMETERS DELIVERED			
Wavelength:	☐ 800-835 nm (IR)	Emission mode:	☐ Continuous ☐ Pulsed
Target fluence:	3 J/cm²	Irradiance:	___ mW/cm²
Exposure time/position:	___ seconds	Application distance:	___ mm

ANATOMICAL AREAS TREATED			
Skin surface area extracted from the TPS dosimetric data (skin contours within the irradiation field). Defined at the initial mapping (inclusion), carried over identically unless the RT plan is modified.			
Anatomical site	**Type**	**Treated**	**Surface area (cm²)**
Anterior cervical region	Skin	☐ Yes ☐ No	
Right lateral cervical region	Skin	☐ Yes ☐ No	
Left lateral cervical region	Skin	☐ Yes ☐ No	
Submandibular region	Skin	☐ Yes ☐ No	
TOTAL — Skin surface area (cm²):	**Skin**		
Energy delivered this session (J) = Fluence (3 J/cm²) × Treated surface area (cm²)			
Total skin energy (J):			

CLINICAL ASSESSMENTS	
Radiation dermatitis (NCI-CTCAE v5.0):	Grade: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
	Grade: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
Pain (VAS 0-10):	___ / 10

CO-INTERVENTIONS AND TOLERANCE	
Local co-interventions today	**Immediate PBM tolerance**
☐ Protective film (Mepitel®, Hydrofilm®) ☐ Topical corticosteroid ☐ Mouthwash / sucralfate gel ☐ Local analgesic ☐ Other: _____	☐ No AE ☐ Local discomfort ☐ Sensation of heat ☐ Tingling ☐ Other: _____

MER (radiation therapist) performing the session:		**Signature:**

15.6 List of investigators

LIST OF INVESTIGATORS			
FIRST NAME, SURNAME	**ROLE**	**POSITION**	**CONTACT DETAILS**
Romain, PLOUZE	Coordinating investigator	Radiation therapist	rplouze@cognacq-jay.fr 01.60.64.63.41
Michel, GOZY	Physician investigator in charge of the research	Radiation oncologist, head of department	mgozy@cognacq-jay.fr 01.60.64.61.52
Elena, LIHIOUEL	Co-investigator	Physician - Radiation oncologist	liuteclacri@gmail.com 01.60.64.63.09
Loic, HERMET	Co-investigator	ENT physician	lhermet@cognacq-jay.fr 01.60.64.60.37
Ibrahim, AMIRAT	Co-investigator	Nurse manager	iamirat@cognacq-jay.fr 01.60.64.61.81