Statistical Analysis Plan

Official Title:

Prospective Cohort Evaluating the Determinants of Radiation-Induced Skin Complications in Patients With Head and Neck Cancer Receiving Preventive Photobiomodulation (COH-PBM-3J)

NCT Number: not yet assigned

Unique Protocol ID: 2026-A01480-51 (ID-RCB) — Sponsor protocol code: 2026-03-01

Document Date: September 15, 2026 (protocol version No. 2)

Sponsor: Hôpital Forcilles - Fondation Cognacq-Jay, Route de Servon, 77150 Férolles-Attilly, France

English translation of the French document approved by the CPP Sud-Ouest et Outre-Mer IV (favourable opinion of 06/10/2026)

STATISTICAL ANALYSIS PLAN

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

Section 9 (Statistical aspects) of protocol version No. 2 of 15/09/2026 — English translation

Protocol code: 2026-03-01 — ID-RCB: 2026-A01480-51

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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 ($\alpha = 5\%$), 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.