

Longitudinal study on nutritional profile of oropharyngeal cancer patients according to HPV status: a challenge for the statisticians

E. Morey^{1,2}, *M. Choulli*^{1,2,3,4}, *R. Alvarez*^{5,6}, *X. Wang*^{1,2}, *B. Quirós*^{2,8}, *S. Tous*^{2,8}, *A.R. González-Tampán*^{4,5}, *M.A. Pavón*^{1,9}, *M. Gomà*^{1,10}, *M. Taberna*^{1,5,7}, *R. Mesia*¹¹, *L. Alemany*^{1,2,8}, *M. Oliva*^{5,7}, *M. Mena*^{1,2,8*}, *L. Arribas*^{1,4,5*}

¹fmorey@idibell.cat, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; ²mchoulli@idibell.cat, Infections and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain; ³University of Barcelona, Barcelona, Spain; ⁴Clinical Nutrition Unit, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain; ⁵Head and Neck Cancer Functional Unit, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain; ⁶Medical Oncology Department, Canary University Hospital, San Cristobal de la Laguna, Tenerife, Spain; ⁷Medical Oncology Department, Catalan Institute of Oncology (ICO), ONCOBELL, L'Hospitalet de Llobregat, Barcelona, Spain; ⁸Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain; ⁹Infections and Cancer Laboratory (INCALAB), Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain; ¹⁰Pathology Department, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona; ¹¹Medical Oncology Department, Catalan Institute of Oncology (ICO)-Badalona, B-ARGO group, Barcelona, Spain. (*)**Both authors contributed equally as senior authors.**

Keywords: Human Papillomavirus (HPV), Oropharyngeal Cancer (OPC), longitudinal data.

In the last two decades, Human Papillomavirus (HPV) infection has emerged as a new causal agent for oropharyngeal cancer (OPC), resulting in a significant increase in the proportion of cases attributed to HPV in some world regions. HPV-related OPC patients (pts) have a better prognosis and longer survival compared to pts without the infection. On the other hand, malnutrition is a common problem in OPC pts. Initially nutrition impact symptoms, cause insufficient food intake compromising nutritional status and toxicity during oncological treatment, and can exacerbate malnutrition. The aim of this study was to assess and compare the nutritional status (NS) of pts regarding their HPV status, using nutritional parameters. At a statistical level, our aim was to understand and take into account the limitations of a longitudinal retrospective study.

A retrospective cohort of primary OPC pts treated with curative intent at the Catalan Institute of Oncology from 2016 to 2020 was recruited. We examined their nutritional, body composition and anthropometric parameters at three time points: at baseline, at three months and at six months after treatment (trt). Firstly, a sensitivity analysis was carried out to identify the bias caused by excluding pts because they did not have anthropometric data at baseline. Secondly, another sensitivity analysis was done to determine how the characteristic of the sample was affected by the losses in the follow-up. Finally, descriptive analysis was performed to explore the differences regarding HPV status of OPC pts at each time point and across the follow-up time. Sankey diagrams among nutritional support and assessment by HPV status were created to illustrate the dynamic flow of pts through time.

Initial recruited number of pts was 131. Pts with anthropometric data were 102. Sensitivity analysis comparing pts with and without anthropometric data showed a higher proportion of pts with initial stages (60.7% vs 34.3%, $p=0.026$) and surgery +/- CT/RT trt (51.7% vs 7.8%, $p<0.001$) in the excluded group. The number of pts with information at the baseline and at three months after trt was reduced at 71, observing that a higher proportion of pts with surgery +/- CT/RT trt continued being excluded.

Finally, the number of OPC pts included in the analysis was 71; 33 (46.5%) were HPV-related (HPV DNA and p16^{INK4a} positive). HPV negative pts were significantly older, more smokers, drinkers than HPV-related OPC pts. Nutritionally, at baseline, HPV-related pts had a higher body mass index (BMI) (median: 27.3 vs 21.8 kg/m², $p<0.001$), and better NS (60.6% vs 26.3%, $p=0.005$). Conversely, after three months after trt, HPV-related pts reduced their BMI compared to baseline (median BMI for HPV-related: 27.3 at baseline vs 24.7 at three months, $p=0.026$, median BMI for HPV negative: 21.8 at baseline vs 20.6 at three months, $p=0.223$). At six months after trt, HPV negative and HPV-related OPC pts maintained similar BMI.

In conclusion, longitudinal data collected retrospectively involve a diversity of limitations that need to be clarified to correctly infer the results obtained. Longitudinal studies denote the importance of understanding the whole process: when, who, how and what information was collected for each patient to know if the selection is (and how) affecting the results. Only then, this knowledge can be helpful in the nutritional management of these pts. Nevertheless, more research is needed to better understand the changes observed.