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**Performance of dual p16 and HPV testing for determining prognosis in cancer of the oropharynx, the EPIC-OPC Study**

H. Mehanna<sup>1</sup>, M. Taberna Sanz<sup>2</sup>, S. Tous<sup>3</sup>, J. Brooks<sup>1</sup>, C. von Buchwald<sup>4</sup>, M. Mena<sup>5</sup>, N. Batis<sup>1</sup>, R.H. Brakenhoff<sup>6</sup>, R. Baatenburg de Jong<sup>7</sup>, J.P. Klussmann<sup>8</sup>, T. Dalianis<sup>9</sup>, H. Mirghani<sup>10</sup>, A. Schache<sup>11</sup>, J.A. James<sup>12</sup>, S.H. Huang<sup>13</sup>, M.A. Broglie<sup>14</sup>, M. Hoffmann<sup>15</sup>, L. Alemany<sup>3</sup>

<sup>1</sup> Institute of Cancer and Genomic Sciences Robert Aitken Building, The University of Birmingham Institute for Cancer Studies, Birmingham, UK, <sup>2</sup> Medical Oncology Department, Head and Neck Cancer Unit, Institut Català d'Oncologia-Hospital Duran i Reynals, Hospitalet de Llobregat, Spain, <sup>3</sup> Cancer Epidemiology Research Program, Institut Català d'Oncologia-Hospital Duran i Reynals, Hospitalet de Llobregat, Spain, <sup>4</sup> Department of Otolaryngology, Head and Neck Surgery, Faculty of Health and Medicine Sciences, University of Copenhagen, Copenhagen, Denmark, <sup>5</sup> Cancer Epidemiology Research Program (CERP), Institut Català d'Oncologia (ICO) - Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet de Llobregat, Spain, <sup>6</sup> Department of Otolaryngology/Head and Neck Surgery, VUmc Cancer Center Amsterdam, Amsterdam, Netherlands, <sup>7</sup> Department of Otorhinolaryngology, Head and Neck Surgery, ErasmusMC Cancer Center, Rotterdam, Netherlands, <sup>8</sup> Department of Otorhinolaryngology, Head and Neck Surgery, University of Giessen, Giessen, Germany, <sup>9</sup> Oncology – Pathology, Cancer Center Karolinska, Stockholm, Sweden, <sup>10</sup> Department of Head and Neck Oncology, Gustave Roussy Cancer Campus, Villejuif, France, <sup>11</sup> Department of Molecular and Clinical Cancer Medicine, University of Liverpool Cancer Research Centre Roy Castle Building, Liverpool, UK, <sup>12</sup> Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK, <sup>13</sup> Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, <sup>14</sup> Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Zurich, Zurich, Switzerland <sup>15</sup> Department of Otorhinolaryngology, Head and Neck Surgery, Christian-Albrechts-University Kiel, Kiel, Germany

**Background**

p16<sup>INK4a</sup> (p16) immunostaining is the most widely implemented technique in clinical settings for determining HPV causation and HPV-related prognosis biomarker of oropharyngeal cancer (OPC). A subset of p16+ OPC are HPV-; and their prognosis is still unclear. The aim of this study is to clearly define the proportion, determinants and prognosis of OPC patients who are p16+/HPV-.

**Methods**

We established an international consortium comprising 13 cohorts of OPC patients with data on p16, HPV, demographics, tobacco/alcohol use and clinical data. A centralized individual patient data reanalysis was performed. Multivariate models were used to evaluate factors associated with HPV status as defined by different HPV-assessment methods. Proportional-hazards models were used to compare the risk of death (OS) among HPV-related and un-related OPC.

**Results**

In total 7702 patients from 9 different countries were included. The percentage of positive cases was 49.7%, 47.9% and 44.3% for p16+, HPV+ and p16+/HPV+, respectively. Among p16+ cases, 10.9% were HPV-. This proportion differed significantly by cohorts and geographic areas (p-value<0.001) and was lowest in the highest prevalence areas (Table). Compared to p16-/HPV- tumors, p16+/HPV+ was the biomarker with strongest prognostic value (aHR 0.28, 95%CI 0.25-0.31), followed by p16+/HPV- (aHR=0.65, 95%CI 0.56-0.76), and p16-/HPV+ (HR=0.72, 95%CI 0.60-0.86). Disease-free/OPC-specific survival analyses will be presented at the congress. Table: 9110

p16+/HPV- by region and cohort from the EPIC-OPC study

Region/Cohort	Total N	NP16+ N	P16+/HPV- N	(%)*
North America	186	135	2	1.5
Canada-Toronto	186	135	2	1.5
Northern Europe	6380	3320	351	10.6
Denmark-Copenhagen	2169	1324	123	9.3
UK-Birmingham	816	499	58	11.6
UK-Liverpool	252	152	12	7.9
UK-Belfast	232	95	11	11.6

Region/Cohort	Total N	P16+ N	HPV- N	P16+/HPV- (%)*
The Netherlands-Amsterdam/Rotterdam	1203	388	48	12.4
Germany-Giessen	704	235	40	17.0
Germany-Cologne	205	111	17	15.3
Germany-Kiel	126	58	11	19.0
Sweden-Stockholm	539	375	24	6.4
Switzerland-Zurich	134	83	7	8.4
Southern Europe	1136	370	63	17.0
France-Paris	275	275	275	12.7
Spain-Barcelona	861	95	28	29.5
All	7702	3825	416	10.9

\*p16+/HPV- percent among p16 tested.

## Conclusions

p16+/HPV+ tumors showed the highest OS magnitude of association compared with other biomarkers combinations. Using p16 immunostaining alone, 11% OPC patients would be incorrectly classified as HPV-related OPC according to TNM-8 staging, and with risk of misclassification for de-escalation in clinical trials, particularly in regions with lower attributable fractions of HPV.

## Legal entity responsible for the study

Catalan Institute of Oncology.

## Funding

Has not received any funding.

## Disclosure

All authors have declared no conflicts of interest.

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