Reviewer's report

Title: Human Papillomavirus-associated oropharyngeal cancer: an observational study of diagnosis, prevalence and prognosis in a UK population

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Reviewer: Chung Feng Hwang

Reviewer's report:

The authors performed retrospective review the prevalence of HPV-positive OPC in an unselected UK population and correlate HPV positivity with clinical outcome. HPV was found in 55% of OPCs within the population. Dramatic improvements in loco-regional control and survival were seen in HPV-positives.

Major Compulsory Revisions

1. page 9 Statistical Methods: Analyses of OS and PFS included all patients, irrespective of treatment intent and response to treatment. -> The patient received palliative treatment should be excluded in the beginning because the clinical outcome was worse in this group.

2. page 17 2nd paragraph: This effect is greater than in many clinical trial cohorts, due in part (but not entirely) to the inclusion of palliative patients. -> Palliative patients should not be included in survival analysis.

3. page 19 conclusion: HPV was responsible for the development of 55% of OPCs in this study. -> There were no evidence to support HPV was responsible for the development of 55% of OPCs in the study. The authors only found HPV positivity in 55% OPCs cases.

4. page 19 conclusion: p16 IHC appears most prognostic and is unaffected by sample DNA quality, making it a useful test in clinical practice. -> The difference of p16 was 10% in the study. P16 was also affected by sample DNA quality. The sample size may be too small to reach statistical significance.

Minor Essential Revisions

1. page 6 line 2: in most other H&N cancers -> in most other H&N (head and neck) cancers

2. page 19 1st paragraph: Although patients were identified retrospectively, their clinical and tumour data were recorded prospectively. -> The manuscript also belonged to a retrospective study.

Discretionary Revisions

1. page 7 study population: This cohort represented ~50% of patients diagnosed with OPC during the period; the rest were not identified or excluded because pathology blocks were not retrievable. -> Why were -50% OPC pathological block not retrievable? Were the clinical data and outcome of the rest without
pathological block different form the study population?

2. page 9 p16 immunohistochemistry: p16 IHC was scored as positive if there was strong and diffuse nuclear and cytoplasmic staining present in greater than 70% of the malignant cells. -> The scoring system is subjective and not very popular.

3. page 11 HPV prevalence: Tumours were classified as HPV-positive if they contained HPV DNA (by GP5+/6+PCR and/or ISH) and overexpressed p16. -> This classification was not very popular. I think the prognosis in the HPV DNA positive group was also better than HPV DNA negative group in this study. The 'Equivocal' groups made the study more complicated.

4. page 16 discussion 1st paragraph: P16 expression is not affected by DNA quality and may be utilized as a single marker of HPV infection in clinical practice, -> The p16 expression was also affected by DNA quality (from 57% to 47%). Dose it mean we only measure p16 expression and not need measure HPV infection in the future study?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests