HPV-associated oropharyngeal cancer — discussion points

Peter Goon and Holger Sudhoff

In their recent Review (Lechner, M. et al. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nat. Rev. Clin. Oncol.*, https://doi.org/10.1038/s41571-022-00603-7; 2022)[1], Lechner et al. provide a useful addition to the medical literature. Nonetheless, we would like to raise a few important discussion points. Several reviews (including that of Lechner et al.[1]) have now mentioned that HPV⁺ oropharyngeal cancers do not have a neoplastic–dysplastic phase, and that hence it follows that screening for premalignant lesions and prevention of invasion is not possible[2,3].

For example, in the legend of figure 2 of their Review, the authors mention " … the development of neoplasia (in the cervix this is evident as lesions detectable by screening but no such lesions have been identified in the oropharynx)". This is incorrect. L. Masterson himself (as first author, with M. Lechner and ourselves among the coauthors) demonstrated in 2015 (REF.[4]), using laser capture and microdissection, that it is possible to find, isolate and detect cells of a premalignant dysplastic, or carcinoma in situ, phenotype adjacent to many HPV⁺ oropharyngeal cancers and then perform transcriptomic studies using the mRNA isolated from them. This study[4] showed that a novel biomarker, *SYCP2*, had consistently increased levels of expression, in addition to *SFRP1*, *CRCT1*, *DLG2* and *CRNN*, which also had altered levels of expression compared to the nonmalignant epithelium. This study was the first, to our knowledge, to demonstrate that: (1) population or targeted screening for HPV⁺ oropharyngeal cancer is possible, analogous to the cervical screening model; (2) that novel biomarkers such as those described above could potentially be used for molecular screening; and (3) that the pathogenesis and oncogene addiction profile of HPV-associated oropharyngeal cancer is highly likely to be similar to that of both cervical cancer and HPV⁺ anogenital cancers.

Furthermore, sequencing studies involving samples from patients with head and neck cancers have revealed interesting subgroups, such as patients with HPV⁺ head and neck squamous cell carcinoma (HNSCC), who also have a history of heavy smoking (>10 pack years), and/or betel quid (comprising betel leaf, areca nut, slaked lime and/or tobacco) consumption. A subgroup of these patients have tumours of a mixed pathogenesis, driven by a combination of oncogenic driver alterations and exposure to carcinogens. A whole-exome sequencing analysis from India demonstrates that the mutational burden of HPV⁺ HNSCC (mostly oral squamous cell carcinomas, although the same principle applies to all subgroups) is not significantly different compared to the larger group of patients with HPV⁻ HNSCC; the majority in both groups have exposure to the carcinogens present in betel quid, thus demonstrating the effects of these additional oncogenic drivers[5]. Discussions of some of these newer HPV⁺ HNSCC subgroups, and the relative importance of some of the known risk factors and carcinogen exposures (such as tobacco smoking)[6], within the group of HPV⁺ oropharyngeal cancers would have been a useful addition to Lechner et al.' s Review[1].

In conclusion, we reiterate that Lechner et al.[1] have written an excellent review, apart from the omission of a couple of interesting and important discussion points. No doubt these will be covered in detail in the future. We hope that this Correspondence will help to stimulate debate, discussion and further research for the benefit of all patients with head and neck cancer, both currently and in the future.

There is a reply to this letter by Lechner, M., Liu, J., Masterson L. & Fenton, T. R. *Nat. Rev. Clin. Oncol.*, https://doi.org/10.1038/s41571-022-00627-z (2022).

Peter Goon ✉ and Holger Sudhoff
University Department of Otolaryngology and Head & Neck Surgery, Universität Bielefeld, Bielefeld, Germany.
✉*e-mail: peter.goon@klinikumbielefeld.de*

https://doi.org/10.1038/s41571-022-00626-0

1. Lechner, M., Liu, J., Masterson, L. & Fenton, T. R. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-022-00603-7 (2022).
2. Johnson, D. E. et al. Head and neck squamous cell carcinoma. *Nat. Rev. Dis. Primers* **6**, 92 (2020).
3. Cramer, J. D., Burtness, B., Le, Q. T. & Ferris, R. L. The changing therapeutic landscape of head and neck cancer. *Nat. Rev. Clin. Oncol.* **16**, 669–683 (2019).
4. Masterson, L. et al. Deregulation of SYCP2 predicts early stage human papillomavirus-positive oropharyngeal carcinoma: a prospective whole transcriptome analysis. *Cancer Sci.* **106**, 1568–1575 (2015).
5. India Project Team of the International Cancer Genome Consortium. Mutational landscape of gingivo-buccal oral squamous cell carcinoma reveals new recurrently-mutated genes and molecular subgroups. *Nat. Commun.* **4**, 2873 (2013).
6. Chen, S. Y. et al. The association of smoking and outcomes in HPV-positive oropharyngeal cancer: a systematic review. *Am. J. Otolaryngol.* **41**, 102592 (2020).

Competing interests
The authors declare no competing interests.

Reply to 'HPV-associated oropharyngeal cancer — discussion points'

Matt Lechner, Jacklyn Liu, Liam Masterson and Tim R. Fenton

We thank P. Goon and H. Sudhoff for their erudite feedback on our Review (Lechner, M. et al. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nat. Rev. Clin. Oncol.*, https://doi.org/10.1038/s41571-022-00603-7; 2022)[1], which raises some interesting points of discussion (Goon, P. & Sudhoff, H. HPV-associated oropharyngeal cancer — discussion points. *Nat. Rev. Clin. Oncol.*, https://doi.org/10.1038/s41571-022-00626-0; 2022)[2].

Regarding the first point (the existence of a defined premalignant phase in HPV-associated oropharyngeal carcinoma), we do not disagree with this assertion. The legend of figure 2 of our Review[1] refers to the much larger body of evidence describing a premalignant phase in cervical cancer, as opposed to the smaller research base for oropharyngeal cancer. We agree that identifying premalignant cells and carcinoma in situ located in the vicinity of diagnosed HPV⁺ oropharyngeal cancers is possible, as demonstrated in various publications (including our previous publication with P. Goon and H. Sudhoff[3]); crucially, however, no screening technology or method that enables the routine detection of such lesions in this context is currently available. This lack of a reliable and broadly applicable screening method remains

one of the most pressing unmet clinical needs in this field.

The second issue raised indicates the need for further discussion regarding high-risk subgroups of patients with HPV-associated oropharyngeal carcinoma, such as those with a history of tobacco and/or betel nut exposure. Although we do refer to the additional disease-specific mortality caused by smoking, and the occurrence of *TP53* and smoking-associated *KRAS* mutations of the type seen in lung adenocarcinoma, a more extensive description of molecular changes in these subgroups was beyond the scope of our Review[1], owing to both word-count restrictions and our remit to focus specifically on the oropharynx. We note that the interesting whole-exome sequencing analysis performed in 2013 (REF.[4]) mainly refers to oral cavity carcinoma, which is again beyond the intended scope of our Review[1]. This and other larger whole-exome sequencing studies[5] have defined key head and neck squamous cell carcinoma (HNSCC) driver genes, yet analysis of the entire genomic landscape (whole-genome sequencing) of HNSCC is thus far restricted to the study of 150 HNSCCs (103 of which were HPV$^+$) from Gillison and colleagues[6], which we discussed in some detail in our Review[1]. To this end, the ongoing UK 100K genome project includes a subset of ~300 head and neck cancers, which will be analysed using deep (>100×) whole-genome sequencing (I. Reddin et al., unpublished). We hope that large-scale genomic analyses of HNSCC such as these, in combination with further molecular profiling of potential precursor lesions such as those described previously[3], will inform the development of much-needed early detection strategies.

Matt Lechner[1,2,3]✉, *Jacklyn Liu*[1], *Liam Masterson*[4] *and Tim R. Fenton*[5,6]✉

[1]*UCL Cancer Institute, University College London, London, UK.*

[2]*UCL Head & Neck Academic Centre, Division of Surgery and Interventional Science, University College London, London, UK.*

[3]*Department of ENT, Barts Health NHS Trust, London, UK.*

[4]*Department of ENT, Cambridge University Hospitals NHS Trust, Cambridge, UK.*

[5]*School of Biosciences, University of Kent, Canterbury, UK.*

[6]*School of Cancer Sciences, Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK.*

✉*e-mail: m.lechner@ucl.ac.uk; t.fenton@soton.ac.uk*

https://doi.org/10.1038/s41571-022-00627-z

1. Lechner, M., Liu, J., Masterson, L. & Fenton, T. R. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-022-00603-7 (2022).
2. Goon, P. & Sudhoff, H. HPV-associated oropharyngeal cancer — discussion points. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-022-00626-0 (2022).
3. Masterson, L. et al. Deregulation of SYCP2 predicts early stage human papillomavirus-positive oropharyngeal carcinoma: a prospective whole transcriptome analysis. *Cancer Sci.* **106**, 1568–1575 (2015).
4. India Project Team of the International Cancer Genome Consortium. Mutational landscape of gingivo-buccal oral squamous cell carcinoma reveals new recurrently-mutated genes and molecular subgroups. *Nat. Commun.* **4**, 2873 (2013).
5. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* **517**, 576–582 (2015).
6. Gillison, M. L. et al. Human papillomavirus and the landscape of secondary genetic alterations in oral cancers. *Genome Res.* **29**, 1–17 (2019).

Competing interests

The authors declare no competing interests.