



Pretreatment prognostic factor for patients with human papillomavirus related oropharyngeal cancer

Daisuke Sano, Nobuhiko Oridate

Department of Otorhinolaryngology-Head and Neck Surgery, Yokohama City University, School of Medicine, Yokohama, Japan

Correspondence to: Daisuke Sano, MD, PhD. Department of Otorhinolaryngology-Head and Neck Surgery, Yokohama City University, School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: dsano@yokohama-cu.ac.jp.

Comment on: Floberg JM, DeWees TA, Chin RI, *et al.* Pretreatment metabolic tumor volume as a prognostic factor in HPV-associated oropharyngeal cancer in the context of AJCC 8th edition staging. *Head Neck* 2018;40:2280-7.

Submitted Mar 26, 2019. Accepted for publication Apr 02, 2019.

doi: 10.21037/tcr.2019.04.02

View this article at: <http://dx.doi.org/10.21037/tcr.2019.04.02>

In recent years, the incidence of human papillomavirus related oropharyngeal cancer (HPV-OPC) has been increased worldwide (1). Although HPV-OPC often has advanced nodal disease, many patients with HPV-OPC are younger and have better response rates to treatment, resulting in better prognosis compared to traditional alcohol- and smoking-related OPC (2). Thus, HPV infection status is now well known as one of the most significant prognostic factors in OPC patients. Because of such unique clinical characteristics of HPV-OPC and the results of the international multicenter cohort study (3), the 8th edition of the AJCC/UICC TNM staging system has a new TNM classification for HPV-OPC (as p16 positive OPC). In fact, rearrangements of T and N status result in huge clinical down-staging in this new TNM classification for this subset of cancers (4).

Most HPV-OPC thus has favorable outcomes, however, there is a group of p16 positive HPV-OPC patients who have treatment failure, resulting poor prognosis in a real-world clinical practice. Therefore, adequate pretreatment biomarkers to predict the prognosis of those patients are necessary to improve their survival. It has been well known that tobacco smoking history is one of strong prognostic factors of survival for patients with HPV-OPC as reported previously (5,6). In addition, it seems that HPV-OPC patients with huge primary lesion such as T4 and advanced nodal category such as N2c and N3 in the 7th edition of the AJCC/UICC TNM staging system could be also categorized as high risk group as described previously (7,8). Furthermore, Spector and colleagues have presented the significance of matted nodes, defined as 3 nodes abutting one another with loss of intervening fat plane accompanied with replacement of

evidence with extracapsular spread status, as a poor prognostic marker in patients with HPV-OPC (9,10). Hence, advanced nodal lesion still could have the significance on prognosis of patients with HPV-OPC. In fact, our single-center prospective cohort study also presented that matted nodes status was an independent prognostic factor for progression-free survival of Japanese patients with HPV-OPC (11).

In this report, Floberg and colleagues conducted a retrospective study of 153 HPV-OPC patients treated with postoperative or definitive radiotherapy. The authors determined total (primary + nodal) metabolic tumor volume (MTV) as an optimal prognostic factor for survival and presented the prognostic significance of pretreatment MTV independent of the 8th edition of the AJCC/UICC TNM staging system in their retrospective study (12). The use of ^{18}F -labeled fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) and fusion images of PET with computed tomography (PET/CT) (13) has become one of routine image examinations to evaluate clinical stage of head and neck cancer including HPV-OPC (14). Among image parameters of ^{18}F -FDG PET, MTV is a volumetric parameter, reflecting tri-dimensional extent as well as the biological activity of the whole tumor, and has been reported as better predictive FDG parameter compared to maximum standardized uptake value (SUVmax) (15).

We previously evaluated the prognostic value of the MTV of patients with laryngeal carcinoma treated by radiotherapy or chemo-radiotherapy as a single institutional prospective cohort study, and presented that MTV of the primary tumor was a significant prognostic factor for disease-free survival of those patients. In addition, we also demonstrated that a

surgery-based treatment showed better relapse-free overall survival compared to radiation-based treatment in laryngeal cancer patients with high MTV. Thus, pretreatment MTV could be useful to predict survival as well as in planning the treatment strategy in patients with head and neck cancer. Floberg and colleagues in this study presented the impact of high MTV as a prognostic factor for survival and recurrence of HPV-OPC, suggesting that high MTV could also reflect high proliferation ability of HPV-OPC cells. While the authors presented total MTV including both primary and cervical neck disease as an optimal prognostic factor, high total MTV might have the potential to include poor prognostic factors related with advanced primary lesion and/or nodal disease such as matted nodes.

As HPV-OPC patients are generally younger, healthier and have good prognosis, long-term treatment side effect and treatment impact on quality of life for these patients need to be considered. Following these backgrounds of HPV-OPC patients, there has been many ongoing clinical studies to evaluate the applicability of de-escalating treatment of patients with HPV-OPC (16-18) including the substitution of cisplatin by cetuximab on radiotherapy, less aggressive radiation/chemoradiation regimens and less invasive surgery using transoral approach with or without postoperative radiotherapy. Recently, the results of two clinical trials related with these de-intensified treatments in HPV-OPC have been published. Mehanna and colleagues performed an open-label randomised controlled phase 3 trial known as De-ESCALaTE HPV (19) to examine the substitution of cisplatin with cetuximab on radiotherapy in advanced HPV-OPC patients with no or a few tobacco smoking history (less than 10 pack-years) using overall severe toxicity events at two years from the end of treatment as primary outcome measure. In this trial, 166 in the cisplatin group and 168 in the cetuximab group were enrolled and there was no difference in overall severe toxicity between these two groups. Surprisingly, they demonstrated that the cetuximab group showed significantly worse 2-year overall survival and disease recurrence rate compared with the cisplatin group. Gillison and colleagues performed a randomised, multicenter, non-inferiority trial known as NRG Oncology RTOG 1016 (20) to examine if cetuximab could have any potential to maintain a high treatment outcome and reduce toxicity for low-risk HPV-OPC patients. In this trial, 406 in the cisplatin group and 399 in the cetuximab group were eligible and there was no difference in severe toxicity between these two groups. They also demonstrated

that the cetuximab group did not meet the non-inferiority criteria for overall survival and showed significantly worse 5-year progression-free survival compared with the cisplatin group. Thus, the substitution of cisplatin with cetuximab radiotherapy could not show any benefit of both reduced toxicity and tumor control in patients with advanced HPV-OPC. The results of these trials suggest that the establishment of de-escalated treatment without worse cancer control is potentially difficult even in HPV-OPC. Pretreatment prognostic factor such as MTV might be useful as its potential significance for risk stratification of HPV-OPC and de-escalated treatment.

Most clinical examinations using ^{18}F -FDG PET have been conducted as a retrospective review from a single institution's experience, since PET/CT devices have different setting in resolution in each institution. As the authors noted in the discussion of this study, the significance of prognostic value of MTV are required to be validated in a larger cohort, however, the standardization of setting for PET/CT in resolution for a prospective randomized trial might be difficult. Regardless of this kind of limitation, MTV could have an advantage as a prognostic factor, as it is a simple and easily obtained imaging marker. Further studies would be required to determine the detail of the underlying molecular mechanisms of HPV-OPC including biological importance of high MTV tumor cells, leading to more optimal preventive and novel treatment strategies for patients with HPV-OPC in the future.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.04.02>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294-301.
2. Marur S, D'Souza G, Westra WH, et al. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol* 2010;11:781-9.
3. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol* 2016;17:440-51.
4. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017;67:122-37.
5. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
6. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. *J Clin Oncol* 2012;30:2102-11.
7. Huang SH, Xu W, Waldron J, et al. Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas. *J Clin Oncol* 2015;33:836-45.
8. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol* 2013;31:543-50.
9. Spector ME, Gallagher KK, Light E, et al. Matted nodes: poor prognostic marker in oropharyngeal squamous cell carcinoma independent of HPV and EGFR status. *Head Neck* 2012;34:1727-33.
10. Spector ME, Chinn SB, Bellile E, et al. Matted nodes as a predictor of distant metastasis in advanced-stage III/IV oropharyngeal squamous cell carcinoma. *Head Neck* 2016;38:184-90.
11. Sano D, Yabuki K, Arai Y, et al. The applicability of new TNM classification for human papilloma virus-related oropharyngeal cancer in the 8th edition of the AJCC/UICC TNM staging system in Japan: A single-centre study. *Auris Nasus Larynx* 2018;45:558-65.
12. Floberg JM, DeWees TA, Chin RI, et al. Pretreatment metabolic tumor volume as a prognostic factor in HPV-associated oropharyngeal cancer in the context of AJCC 8th edition staging. *Head Neck* 2018;40:2280-7.
13. Paidpally V, Chirindel A, Lam S, et al. FDG-PET/CT imaging biomarkers in head and neck squamous cell carcinoma. *Imaging Med* 2012;4:633-47.
14. Fletcher JW, Djulbegovic B, Soares HP, et al. Recommendations on the use of 18F-FDG PET in oncology. *J Nucl Med* 2008;49:480-508.
15. Park GC, Kim JS, Roh JL, et al. Prognostic value of metabolic tumor volume measured by 18F-FDG PET/CT in advanced-stage squamous cell carcinoma of the larynx and hypopharynx. *Ann Oncol* 2013;24:208-14.
16. Masterson L, Moualed D, Liu ZW, et al. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma: a systematic review and meta-analysis of current clinical trials. *Eur J Cancer* 2014;50:2636-48.
17. Taberna M, Mena M, Pavon MA, et al. Human papillomavirus-related oropharyngeal cancer. *Ann Oncol* 2017;28:2386-98.
18. Mirghani H, Blanchard P. Treatment de-escalation for HPV-driven oropharyngeal cancer: Where do we stand? *Clin Transl Radiat Oncol* 2017;8:4-11.
19. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCaLaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019;393:51-60.
20. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019;393:40-50.

Cite this article as: Sano D, Oridate N. Pretreatment prognostic factor for patients with human papillomavirus related oropharyngeal cancer. *Transl Cancer Res* 2019;8(2):354-356. doi: 10.21037/tcr.2019.04.02