Open Peer Review on Qeios

[Commentary] Implications of HPV infectivity in early diagnosis and treatment of advanced/recurrent malignancies

Takuma Hayashi[1], Ikuo Konishi[2]

1 Kyoto Medical Center

2 Japan Agency for Medical Research and Development (AMED)

Funding: Japan Society for the Promotion of Science for TH (Grant No. 19K09840, No. 23K08881), START-program Japan Science and Technology Agency (JST) for TH (grant No. STSC20001) and National Hospital Organization Multicenter clinical study for TH (grant No. 2019-Cancer in general-02), The Japan Agency for Medical Research and Development (AMED) (Grant No. 22ym0126802j0001).

Potential competing interests: No potential competing interests to declare.

Abstract

Infection with HPV genotypes is a cause of cervical and pharyngeal cancer,*etc*. The amount of circulating HPV DNA in the blood is useful for detecting advanced/recurrent cancer earlier than the rise in tumor markers. Compared to HPV infection-negative cancer, cancer immunotherapy is more effective for HPV infection-positive cancer.

Dr. Takuma Hayashi[1,2,*], and **Dr. Ikuo Konishi**[1,2,3]

[1] *Cancer Medicine, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan*

[2] *Medical R&D Promotion Project, The Japan Agency for Medical Research and Development (AMED), Tokyo, Japan.*

[3] *Kyoto University Graduate School of Medicine, Kyoto, Japan.*

[*]**Corresponding author**: Correspondence to Takuma Hayashi. Cancer Medicine, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihatake-cho, Fukakusa, Fushimi-ku, Kyoto City, Kyoto 612-8555, Japan. E-mail: yoyoyo224@hotmail.com.

Short title: Diagnosis and treatment for HPV-positive malignancy

Keywords: HPV, diagnosis, treatment, malignancy, advanced, recurrent.

Human papillomavirus (HPV) is a virus that causes sexually transmitted diseases and skin diseases. The main route of transmission of HPV is sexual intercourse (sex, oral sex, anal sex) [1]. Latent HPV infection is established when HPV enters the basal cells from a small wound on the genitals. Sexually transmitted HPV infection is associated with the development of benign condyloma acuminata, as well as pharyngeal cancer, cervical cancer (including vaginal cancer), anus cancer, and penile cancer [1]. In most HPV-infected people, HPV is eliminated by the host immune system, which protects the body from foreign enemies. However, in rare cases, HPV infections have been observed to persist for long

periods of time without the elimination of HPV. The results of clinical research and basic medical research to date have revealed that normal cells gradually become cancerous due to persistent HPV infection.

HPV vaccines prevent persistent infection with certain types of HPV. In clinical practice, three HPV vaccines are prescribed: the bivalent "Cervarix" (GlaxoSmithKline K.K., London, UK), the tetravalent "Gardasil" (Merck), and the nine-valent "Sylgard 9" (Merck KGaA, Darmstadt, Germany). In clinical trials conducted in various countries, it has been revealed that the development of pharyngeal, cervical (including vaginal), anal, and penile cancers, as well as the benign disease Condyloma acuminata, is prevented by the inoculation of the 4-valent HPV vaccine or the 9-valent HPV vaccine [2]. Globally, infections with HPV types 16 and 18 account for approximately 70% of all cervical cancers.

During the period from December 2019 to January 2023, the treatment methods for a total of 2891 cases (OncoGuide™ NCC oncopanel test: 763 cases, FoundationOne® CDx test: 2128 cases) were examined in cancer genomic medicine at Japanese national universities. A total of 36 cases of advanced pharyngeal cancer, 104 cases of advanced cervical cancer, 22 cases of advanced anus cancer, and 10 cases of advanced penile cancer were studied in cancer genomic medicine in Japan. From the results of the cancer genomic tests, it was revealed that a positive HPV16 or HPV18 infection was detected in a total of 11 cases (11/36, 30.6%) of advanced pharyngeal cancer, 37 cases (37/104, 35.6%) of advanced cervical cancer, 8 cases (8/22, 36.4%) of advanced anus cancer, and 3 cases (3/10, 30.0%) of advanced penile cancer. Previous clinical trials have investigated the efficacy of nivolumab in 11 cases of HPV-positive pharyngeal cancer and 25 cases of HPV-negative pharyngeal cancer. The results showed that nivolumab was more effective in treating 11 patients with HPV-positive throat cancer compared to 25 patients with HPV-negative throat cancer [3][4]. It has been shown that the efficacy of immune checkpoint inhibitors such as nivolumab is significantly higher in malignant tumors with a high tumor mutation burden (TMB) or Microsatellite Instability (MSI) high. Therefore, the possibility that HPV infection increases TMB and/or MSI in malignant cells of tumors is being investigated. Based on these clinical findings, the clinical application of novel anti-tumor immunotherapy, which involves infecting malignant tumors with pseudoviruses and increasing anti-immunogenicity against malignant tumors, is being considered [5][6].

In medical care in Japan, cancer genomic testing is performed on patients with advanced cancers to whom standard treatments or recommended treatments for the various types of cancer are not applicable. Therefore, the infection rate of HPV16 or HPV18 in advanced cancer, as shown above, is different from the incidence of cancer due to HPV infection in Japanese people. However, if HPV vaccination becomes widespread among Japanese people, the prevalence of cancer caused by infection with HPV16 or HPV18 (i.e., pharyngeal cancer, cervical cancer, and anus cancer) is expected to decrease considerably. According to the results of clinical studies, the number of cases of HPV-infected pharyngeal cancer in men is approximately three times the number of cases of HPV-infected pharyngeal cancer in women. Therefore, HPV vaccination for men must also be widely available [7].

Recent clinical research results show that the recurrence of various malignant tumors can be confirmed earlier by detecting circulating DNA (cDNA) in the blood derived from malignant tumor cells, rather than by increasing the tumor marker values [8]. Therefore, it has been reported that the recurrence of HPV-infectious malignant tumors is confirmed earlier by the detection of tumor-derived circulating HPV genes in the blood rather than by increased tumor marker

values [9] (Figure 1). In other words, tumor-derived circulating HPV DNA is useful as a marker for detecting the recurrence of malignant tumors more than the elevation of existing tumor markers.

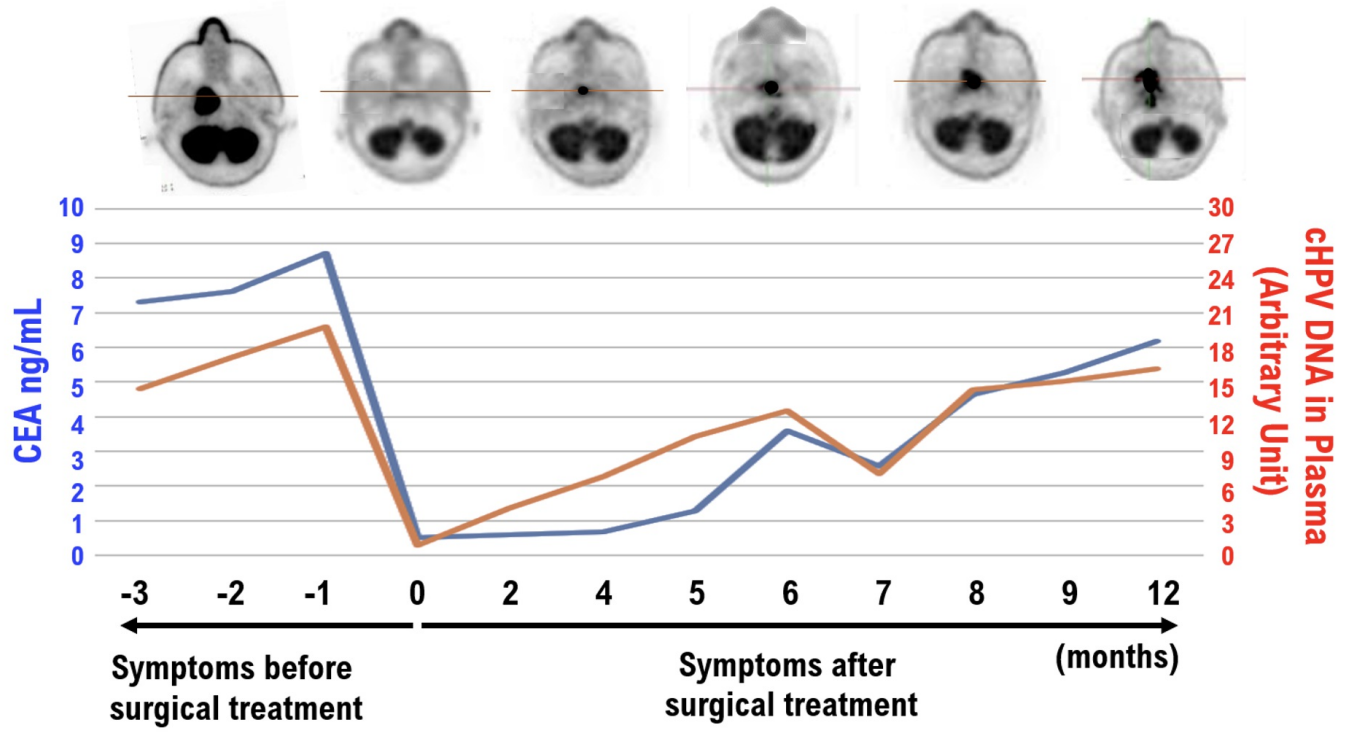

Figure 1. Early diagnosis of advanced/recurrent malignant tumors by the detection of circulating HPV DNA rather than elevated tumor marker values

Human oncogenes such as Kirsten murine sarcoma virus (KRAS) are well known as oncogenes derived from viral genes. As described above, various malignant tumors caused by viral infection have been recognized. Vaccination is effective in preventing viral infection. However, unlike bacteria, mutations in viral genes easily change the structure of the viral backbone proteins and structural proteins. Therefore, it has become a problem that the preventive effect of vaccines against viral infections is reduced. Therefore, there is a need to produce vaccines that induce the production of antiviral antibodies that recognize the structural proteins of mutant virus variants.

Conclusion

Unlike the treatment of bacterial infections by prescribing antibiotics, humans have struggled to prevent viral infections through vaccination and to treat them with drugs due to repeated mutations in the genes of the viruses themselves. However, since malignant tumors are infected with HPV, the effectiveness of cancer immunotherapy has increased. In addition, circulating HPV DNA detection is more effective than elevated tumor marker values for the early diagnosis of advanced/recurrent malignant tumors. As described above, advances in medical technology have enabled the early diagnosis and treatment of advanced/recurrent malignant tumors and are expected to lead to better innovations in medical technology.

Statements and Declarations

Disclaimer: The material (manuscript and figure) is original research. It has not been previously published and has not been submitted for publication elsewhere while under consideration.

Data availability: This manuscript is an editorial and does not contain research data. Therefore, there are no research data or information to be published or opened.

Acknowledgements: We thank all the medical staff and co-medical staff for providing and helping with medical research at the National Hospital Organization Kyoto Medical Center. We appreciate Crimson Interactive Japan Co., Ltd., for revising and polishing our manuscript in the native English language.

Funding: This research comment was performed with the support of the following research funding: Japan Society for the Promotion of Science for TH (Grant No. 19K09840, No. 23K08881), the START program of the Japan Science and Technology Agency (JST) for TH (grant No. STSC20001), and the National Hospital Organization Multicenter Clinical Study for TH (grant No. 2019-Cancer in general-02), The Japan Agency for Medical Research and Development (AMED) (Grant No. 22ym0126802j0001).

Contributions: TH wrote the manuscript. IK carefully reviewed the manuscript and commented on aspects of clinical medicine. IK shared information on clinical medicine and oversaw the entirety of the study.

Competing interests: The authors declare no competing interests.

References

1. [a, b]*Scudellari M. HPV: Sex, cancer and a virus. Nature. 2013 Nov 21;503(7476):330-2. doi: 10.1038/503330a.*
2. [^]*Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, Moreira ED Jr, Ngan Y, Petersen LK, Lazcano-Ponce E, Pitisuttithum P, Restrepo JA, Stuart G, Woelber L, Yang YC, Cuzick J, Garland SM, Huh W, Kjaer SK, Bautista OM, Chan IS, Chen J, Gesser R, Moeller E, Ritter M, Vuocolo S, Luxembourg A A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women.; Broad Spectrum HPV Vaccine Study. N Engl J Med. 2015 Feb 19;372(8):711-23. doi: 10.1056/NEJMoa1405044.*
3. [^]*Ferris R, Gillison ML. Nivolumab for Squamous-Cell Cancer of Head and Neck. N Engl J Med. 2017 Feb 9;376(6):596. doi: 10.1056/NEJMc1615565.*
4. [^]*Hayashi T, Konishi I. The Effect of mRNA-Based COVID-19 Vaccination on Anti-Programmed Cell Death Protein 1 Blockade for Nasopharyngeal Cancer May Differ From a Virus-Inactivated Vaccine. World J Oncol. 2023 Aug;14(4):316-320. doi: 10.14740/wjon1620*
5. [^]*Tsang ES, Munster PN. Vaccinia (Smallpox) for the Treatment of Ovarian Cancer-Turning an Old Foe Into a Friend? JAMA Oncol. 2023 Jul 1;9(7):894-896. doi: 10.1001/jamaoncol.2023.0983.*
6. [^]*Holloway RW, Mendivil AA, Kendrick JE, Abaid LN, Brown JV, LeBlanc J, McKenzie ND, Mori KM, Ahmad S. Clinical*

Activity of Olvimulogene Nanivacirepvec-Primed Immunochemotherapy in Heavily Pretreated Patients With Platinum-Resistant or Platinum-Refractory Ovarian Cancer: The Nonrandomized Phase 2 VIRO-15 Clinical Trial. JAMA Oncol. 2023 Jul 1;9(7):903-908. doi: 10.1001/jamaoncol.2023.1007.

7. ^*Green A. HPV vaccine to be offered to boys in England. Lancet. 2018 Aug 4;392(10145):374. doi: 10.1016/S0140-6736(18)31728-8.*
8. ^*Cohen SA, Liu MC, Aleshin A. Practical recommendations for using ctDNA in clinical decision making. Nature. 2023 Jul;619(7969):259-268. doi: 10.1038/s41586-023-06225-y.*
9. ^*Lang Kuhs KA, Brenner JC, Holsinger FC, Rettig EM. Circulating Tumor HPV DNA for Surveillance of HPV-Positive Oropharyngeal Squamous Cell Carcinoma: A Narrative Review. JAMA Oncol. 2023 Oct 12. doi: 10.1001/jamaoncol.2023.4042.*