Oral Oncology 97 (2019) 146–148

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

Successful control of T4 and N3 human papillomavirus-related oropharyngeal squamous cell carcinoma after de-intensified chemoradiotherapy: Report of two cases

ARTICLE INFO

Keywords:
Oropharyngeal neoplasms
Papillomavirus infections
Chemoradiotherapy
Radiation dosage
Treatment outcome

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is causatively divided into two types: human papillomavirus (HPV)-related and HPV-unrelated. Chemoradiotherapy, which results in severe late toxicities leading to impaired quality of life (QOL) [1], remains the standard treatment option for locally advanced OPSCC, irrespective of HPV status [2,3]. Because patients with HPV-related OPSCC survive significantly longer than those with HPV-unrelated OPSCC [4], patients with locally advanced HPV-related OPSCC have to endure an impaired QOL for a long time after standard treatment. De-intensified treatment is expected to improve QOL without compromising survival in patients with locally advanced HPV-related OPSCC, and clinical trials to address its efficacy are ongoing [5]. However, patients with T4 and/or N3 disease are considered poor candidates for de-intensified treatment because they are at high risk of treatment failure [6]. We reviewed patients' charts at Osaka University Hospital and Osaka Rosai Hospital to identify patients with locally advanced OPSCC who discontinued chemoradiotherapy at less than 60 Gy due to adverse events, who, in turn, received de-intensified treatment unintendedly. We found two such patients, and their disease was T4 and/or N3 and HPV-related OPSCC. Surprisingly, they have remained disease-free over a long period after discontinuing treatment.

Case 1

A 71-year-old woman was referred to Osaka University Hospital in October 2013 with trismus and dysphagia. She had no history of smoking. She had experienced repeated compression fractures of the thoracolumbar vertebrae, that led to severe kyphoscoliosis. Upon inspection, she had a tumor extending from the right palatine tonsil to the right lateral wall of the nasopharynx, resulting in otitis media with effusion. Another mass was palpable in the right upper neck, which was speculated to cause ipsilateral hypoglossal nerve palsy. The primary tumor was biopsied, and the patient underwent imaging test, including contrast-enhanced computed tomography (CE-CT) and ^{18}F-fluorodeoxyglucose positron-emission tomography-CT (FDG PET-CT). Histopathological analysis and immunohistochemistry for p16 was performed on the biopsy sepcimen. In addition, sequencing of HPV DNA was performed [7]. The patient was diagnosed with p16-positive/HPV type 16 DNA-positive cT4bN2cM0 OPSCC (Fig. 1) according to the 7th edition of the International Union Against Cancer (UICC) staging system [8]. The patient received radiotherapy at 2 Gy/fraction/day, concurrent with weekly 20 mg/m^2 cisplatin (CDDP) and 10 mg/m^2 docetaxel (DOC) at a prescribed dose of 66 Gy for radiotherapy and 6 cycles for chemotherapy (120 mg/m^2 of CDDP and 60 mg/m^2 of DOC) [9]. Due to a newly developed compression fracture, the patient discontinued chemoradiotherapy after completing 56 Gy radiotherapy and 5 chemotherapy cycles (100 mg/m^2 of CDDP and 50 mg/m^2 of DOC). Tumor response was evaluated 11 weeks after discontinuation of the treatment, and no residual tumor was evidenced (Fig. 1). Thereafter she has been monitored periodically by neck CT scans and plain chest radiography scheduled every 6 months. She has had neither locoregional recurrence nor distant metastasis for over 5 years.

Case 2

A 61-year-old man presented to Osaka Rosai Hospital in December 2014 with dysphagia and a sore neck. He was a former smoker with a smoking history of 86 pack-years. He had a pacemaker inserted in his heart because of sick sinus syndrome. A large tumor that originated from the right palatine tonsil was observed. The tumor showed wide invasion to the surrounding structures, including the base of tongue, while his right neck mass was fixed. He received the same clinical workup as that in Case 1. His disease was diagnosed as p16-positive/HPV type 16 DNA-positive cT4aN3M0 OPSCC (Fig. 2). He received chemoradiotherapy of the same regimen as that described in Case 1. During the chemoradiotherapy, he developed severe aspiration pneumonia and was managed at an intensive care unit under intubation. Although he recovered from the pneumonia, the chemoradiotherapy was discontinued after completion of 44 Gy of radiotherapy and 4 chemotherapy cycles (80 mg/m^2 of CDDP and 40 mg m^2 of DOC). FDG PET-CT taken at 11 weeks after termination of the treatment showed complete metabolic response of the primary tumor with an equivocal metabolic response of cervical node metastasis. CE-CT at 6 months after termination of the treatment and showed no evidence of residual and/or recurrent disease (Fig. 2), and the patient remained disease-free for more than 4 years.

https://doi.org/10.1016/j.oraloncology.2019.08.009
Received 12 July 2019; Received in revised form 6 August 2019; Accepted 7 August 2019
Available online 20 August 2019
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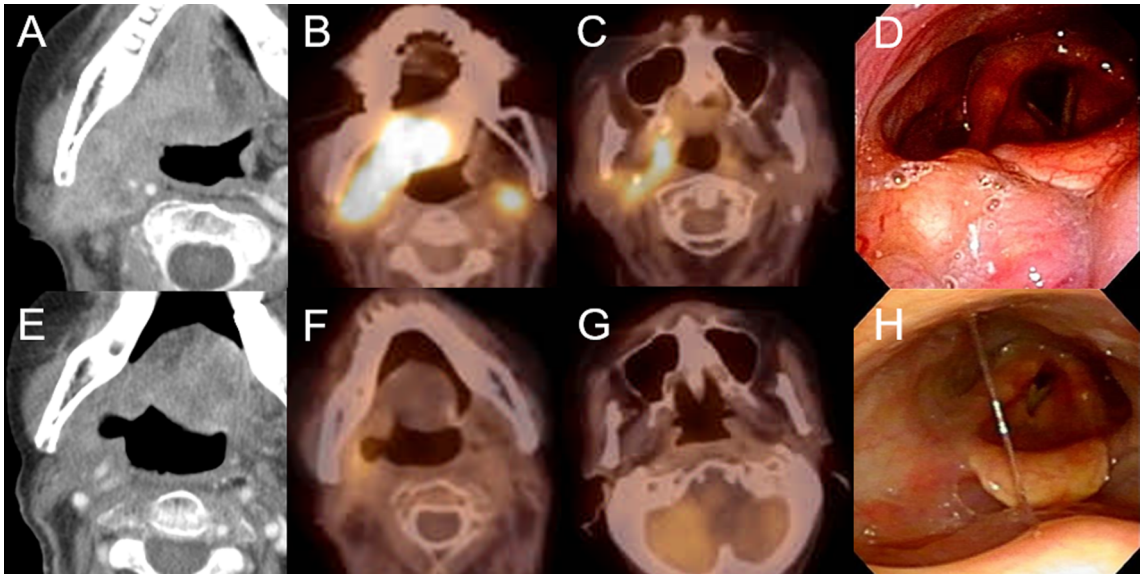

Fig. 1. Images from Case 1 before treatment (A–D) and at 11 weeks after treatment (E–H). A and E represent contrast-enhanced computed tomography (CT) images; B, C, F and G represent ^{18}F-fluorodeoxyglucose positron-emission tomography-CT images; D and H represent endoscopic images. Before treatment, a primary tumor extending from the right palatine tonsil to the surrounding tissue, including the base of the tongue, lateral wall of the nasopharynx, and parapharyngeal space, was evident with bilateral upper neck metastatic nodes (A–D). No residual locoregional disease was evidenced after treatment (E–G). Note minimal pharyngeal residue at 11 weeks after treatment (H).

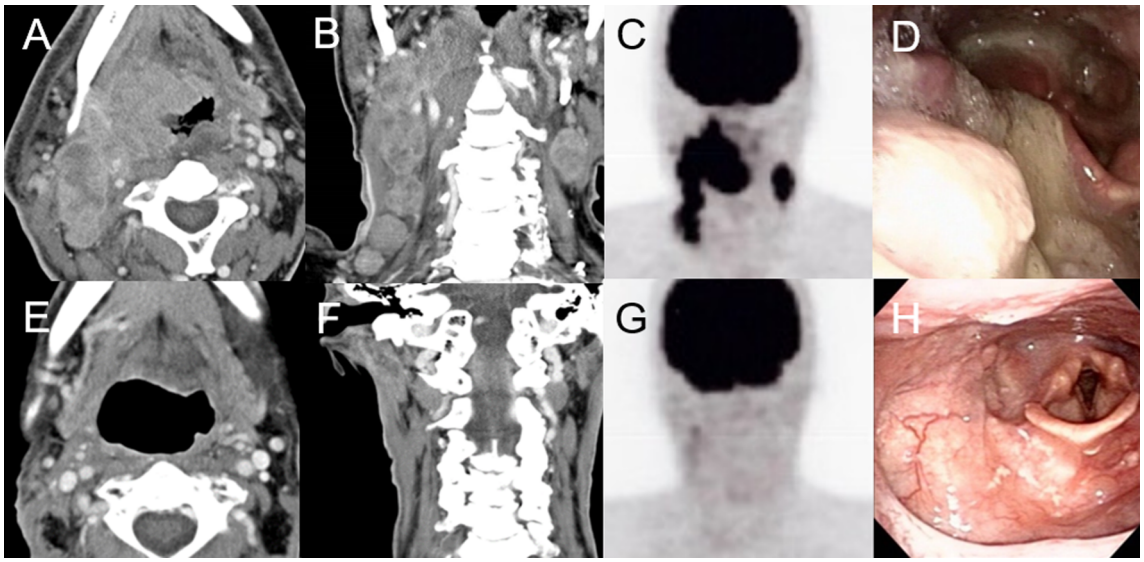

Fig. 2. Images from Case 2 before treatment (A–D), at 11 weeks after treatment (G), and 6 months after treatment (E, F, and H). A, B, E and F represent contrast-enhanced computed tomography (CE-CT) images; C and G represent ^{18}F-fluorodeoxyglucose positron-emission tomography-CT (FDG PET-CT) images, and D and H represent endoscopic images. Before treatment, a right palatine tonsil tumor invading the base of tongue and parapharyngeal space was evident with bilateral multiple neck metastatic nodes (A–D). At 11 weeks after treatment, ipsilateral upper neck residual disease was equivocal on FDG PET-CT, while no residual disease was evidenced on CE-CT 6 months after treatment (E, F). No pharyngeal residue was noted 6 months after treatment (H).

Discussion

Overexpression of p16 is a surrogate marker of HPV infection, and diffuse p16 positivity is regarded to be indicative of HPV-related OPSCC. However, p16-positive OPSCC is not always accompanied by HPV infection. As HPV infection is proved by detection of HPV DNA, p16-positive OPSCC is classified into two subtypes: p16-positive/HPV DNA-positive and p16-positive/HPV DNA-negative [10]. Patients with p16-positive/HPV DNA-negative OPSCC are at higher risk of treatment failure than those with p16-positive/HPV DNA-positive OPSCC [10,11]. A subset of p16-negative OPSCC is also accompanied by HPV infection. However, p16-negative/HPV DNA-positive OPSCC shows less favorable prognosis compared with p16-positive/HPV DNA-positive OPSCC [12]. Collectively, p16-positive/HPV DNA-negative and p16-negative/HPV DNA-positive OPSCCs seem less suitable for de-intensified treatment. Herein, we reported two patients with HPV-related OPSCC who received unintended de-intensified treatment and remained disease-free even after discontinuing chemoradiotherapy. The success of this de-intensified treatment was most likely due to these patients' tumors being p16-positive/HPV DNA-positive. If their tumors had not been p16-positive/HPV DNA- positive, discontinuation of chemoradiotherapy would likely to have led to treatment failure. It is suggested that a subset of patients with T4 and/or N3 p16-positive/HPV DNA-positive OPSCC are likely candidates for de-intensified treatment.

However, no biomarkers exist to identify these patients yet, and biomarkers need to be established that will allow biomarker-driven modifications of treatment intensity for p16-positive/HPV DNA-positive OPSCC. Recently, it was shown that a rapid clearance profile of plasma circulating tumor HPV DNA (ctHPVDNA) during chemoradiotherapy was associated with favorable clinical outcome in HPV-related OPSCC [13]. A rapid clearance of ctHPVDNA may be useful in selecting patients with T4 and/or N3 disease who will benefit from de-intensified treatment.

Acknowledgment

We thank Traci Raley, MS, ELS, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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