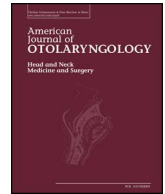




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Prognostic significance of HPV status in the re-irradiation of recurrent and second primary cancers of the head and neck

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ABSTRACT

Purpose: To evaluate the prognostic significance of human papillomavirus (HPV) status among patients treated by salvage radiation therapy for local-regional recurrences and second primary cancers of the head and neck arising in a previously irradiated field.

Methods and materials: The medical records of 54 consecutive patients who underwent re-irradiation for squamous cell carcinoma of the head and neck occurring in a previously irradiated field were reviewed. Only patients with biopsy-proven evidence of recurrent disease that had previously been treated with doses of radiation therapy of at least 60 Gy were included. Determination of HPV status at the time of recurrence was performed by p16 immunohistochemistry. The median age at re-irradiation was 58.5 years (range, 27.9 to 81.5 years). Thirty patients (55.5%) were lifelong never-smokers. The Kaplan Meier method was used to calculate overall survival, progression-free survival, and local-regional control, and distant metastasis-free survival with comparisons between groups performed using the log-rank test.

Results: HPV status among tumors that were re-irradiated was as follows: 16 positive (29.7%); 7 negative (12.9%); 31 unknown (57.4%). The median overall survival in the entire cohort was 11.7 months (range, 8 to 27 months), with the 1-year and 2-year estimates of overall survival being 47.2% and 38.4%, respectively. A statistical trend was identified favoring patients with HPV-positive cancers with respect to the endpoints of overall survival ($p = 0.06$) and progression-free survival ($p = 0.08$) after re-irradiation when compared to the HPV-negative/unknown population. There was no significant difference in distant control between the two cohorts ($p = 0.40$).

Conclusions: The favorable prognostic significance of HPV seemingly extends to patients treated by re-irradiation suggesting that this biomarker may be useful in risk stratification in this setting.

1. Introduction

The incidence of head and neck squamous cell carcinoma (HNSCC) attributed to human papillomavirus (HPV) has risen over the last decade [1]. Although numerous studies have convincingly demonstrated that patients with HPV-positive HNSCC have a more favorable prognosis with at least half the risk of death compared to their counterparts with HPV-negative HNSCC, a significant proportion of the former group nevertheless experience disease progression [2–4]. For patients who develop isolated local-regional failures after initial therapy for HPV-positive HNSCC, treatment options have generally included salvage surgery, re-irradiation, chemotherapy, and/or a combination of each of the above [5]. While data from a recently published subset analysis of two prospective trials conducted by the

Radiation Therapy Oncology Group (RTOG) showed that HPV status remains a strong prognostic factor in the recurrent setting (with a 2-year overall survival rate of 55% in HPV-positive patients compared to 28% in the HPV-negative population), the conclusions did not differentiate between those with local-regional failures, distant metastasis, or both [6]. The purpose of this study was to thus assess the impact of HPV status on survival for patients with local-regionally recurrent HNSCC who underwent re-irradiation with external beam therapy, either as the primary modality or post-operatively after surgery, with the goal of determining whether HPV maintains its prognostic significance in this setting.

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2. Methods and materials

2.1. Study design

This study was approved by the institutional review board at our institution prior to the collection of all patient information. The medical records of 54 consecutive patients who underwent re-irradiation at a large tertiary-care comprehensive cancer center between April 2011 and January 2016 for local-regionally recurrent squamous cell carcinoma of the head and neck occurring in a previously irradiated field were reviewed. Only patients with biopsy-proven evidence of gross recurrent disease that had previously been treated with doses of radiation therapy of at least 60 Gy were included. For all cases, p16 was used as a surrogate for HPV positivity in accordance with standard laboratory guidelines. Notably, p16-testing by immunohistochemistry was repeated whenever possible and confirmed to be positive at the time of recurrence. All patients were re-staged with both magnetic resonance imaging (MRI) and positron emission tomography (PET) at the time of local-regional recurrence. None had evidence of distant metastasis.

2.2. Patients

Among the 54 patients with recurrent HNSCC who underwent re-irradiation and were included in this analysis, HPV status was categorized as positive in 16 (29.6%) and negative/unknown in 38 (70.4%). Thirty-three patients (61%) were male and 21 (39%) were female. The most common primary site of recurrence was the oral cavity ($n = 19$) followed by the oropharynx ($n = 14$). The median age at re-irradiation was 58.5 years (range, 27.9 to 81.5 years) in the entire cohort, 59.6 years (range, 30.9 to 81.5 years) in the HPV-negative/unknown population, and 51.8 years (range, 27.9–75.3 years) in the HPV-positive patients. Smoking history was reliably available for 51 patients, of which 35 (64.8%) had a smoking status of 0 to 10 packs per year and 16 patients (29.6%) had a smoking history of > 10 packs per year. Thirty patients (55.5%) were considered to be lifelong never-smokers. Patient characteristics stratified by HPV status are listed in Table 1.

2.3. Treatment

The median interval between radiation courses for the entire cohort was 20.9 months (range, 2.7 to 322 months). Forty-nine patients underwent re-treatment with intensity-modulated radiotherapy (IMRT) (90.7%) using continuous-course regimens with conventional fractionation, and five (9.2%) patients with stereotactic body radiotherapy (SBRT) with 7–8 Gy fractions delivered on non-consecutive days for 5 treatments over approximately 2 weeks. The median dose of first radiation treatment for all patients was 68.4 Gy (range, 25 to 136 Gy) and the median re-irradiation dose was 60.6 Gy (range, 18 to 70 Gy) for those who underwent retreatment with conventional fractionation. The median re-irradiation dose in the HPV-positive cohort was 60 Gy (range, 60 to 70 Gy) and 62.5 (range, 18 to 70 Gy) in the HPV-negative/unknown cohort. Twenty-three patients (42.6%) underwent surgical resection prior to re-irradiation. Thirty-five patients (64.8%) received concurrent systemic therapy with re-irradiation.

2.4. Endpoints and statistical analysis

Patients were asked to return for a follow-up visit 2 to 3 weeks after completion of re-irradiation and then every 2 to 3 months for the first year, 4 to 6 months for the second year, and then annually thereafter. Local control was judged to have been attained if there was no evidence of tumor progression at the primary site, based on clinical and radiographic findings at follow-up. Regional failure was recorded separately if there was evidence of a cervical or supraclavicular mass distinct from the primary site. Patient follow-up was reported up to the date last seen

Table 1

Patient and treatment characteristics according to HPV status.

	No. of patients (%)		p Value
	HPV-negative/ unknown	HPV-positive	
Sex			
Female	13 (34.2)	8 (50)	
Male	25 (65.8)	8 (50)	
Age			
Median (range)	59.6(30.9–81.5)	51.8(27.9–75.3)	0.08
Smoking			
≤ 10 pack-years	22 (57.9)	13 (81.3)	0.3
> 10 pack-years	13 (34.2)	3 (18.8)	
KPS			
< 80	7 (18.4)	6 (37.5)	0.1
≥ 80	31 (81.6)	10 (62.5)	
Recurrence site			
Oral cavity	14 (36.8)	5 (31.3)	0.2
Oropharynx	11 (28.9)	3 (18.8)	
Larynx	5 (13.2)	1 (6.3)	
Neck	2 (5.3)	4 (25)	
NOS	6 (15.8)	3 (18.8)	
Salvage surgery			
Yes	12 (31.6)	11 (68.8)	0.01
No	26 (68.4)	5 (31.3)	
Concurrent systemic therapy			
Yes	26 (68.4)	9 (56.3)	0.3
No	12 (31.6)	7 (43.8)	
Radiation dose (Gy), median (range)			
Initial treatment	69.3 (40.0–136)	63 (25–72)	0.08
Retreatment	62.5 (18–70)	60(60–70)	0.06

in clinic or up to the date of expiration. All events were measured from the last day of radiation therapy. Actuarial estimates of local-regional control, distant metastasis-free survival, and overall survival were calculated using the Kaplan-Meier method.

3. Results

There were no significant differences in age ($p = 0.08$), gender ($p = 0.2$), smoking history, time interval between radiation courses ($p = 0.80$), performance status ($p = 0.10$), and use of concurrent chemotherapy ($p = 0.30$) between the HPV-positive and HPV-negative/unknown cohorts. Patients in the HPV-positive group (68.8%) were more likely to have received surgery prior to re-irradiation than those in the HPV-negative/unknown group (68.8% vs. 31.6%), ($p = 0.01$).

The median overall survival in the entire cohort was 11.7 months (range, 8 to 27 months), with the 1-year and 2-year estimates of overall survival being 47.2% and 38.4%, respectively. Local-regional control was achieved in 17 patients at last follow-up. The median duration of local-regional control was 4.3 months (range, 3.1 to 7.4 months) for the entire cohort, with 1-year local-regional control of 34.3%. The median progression-free survival for all patients was 4.1 months (range, 3 to 7.1) with 1-year progression-free survival of 32.1%. The mean distant metastasis-free survival was 18.5 months and the 1-year distant control rate was 43.3%.

Among the HPV-negative/unknown cohort, the median overall survival was 11.5 months (range, 7.9 to 16.3 months), with a 1-year overall survival rate of 43.3%. The median overall survival in the HPV-positive group was not reached. HPV-positive patients had a notable trend towards improved overall survival after re-irradiation when compared to the HPV-negative/unknown population ($p = 0.06$; Fig. 1). A similar trend was seen in local-regional control ($p = 0.08$) between these two cohorts as shown in Fig. 2. The median progression-free survival on the HPV-positive cohort was 14.0 months compared to 3.5 months in the HPV-negative/unknown group ($p = 0.09$; Fig. 3).

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