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Stereotactic body radiotherapy for recurrent oropharyngeal cancer – Influence of HPV status and smoking history

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SUMMARY

Purpose: HPV status and smoking history stratifies patients into 3 distinct risk groups for survival following definitive chemoradiotherapy. Local-regional recurrences are common patterns of failure across all 3 risk-groups. SBRT ± cetuximab has emerged as a promising salvage strategy for unresectable locally-recurrent, previously-irradiated head-and-neck cancer (rHNC) relative to conventional re-irradiation ± chemotherapy. However the influence of HPV and smoking remains unknown in the setting of re-irradiation.

Methods/materials: Patients ($n = 30$) with rHNC of the oropharynx salvaged with SBRT ± cetuximab from August 2002 through August 2013 were retrospectively reviewed; HPV status was determined based on p16 staining of primary pathology.

Results: At a median follow-up of 10 months for surviving patients, the mean overall survival for all patients was 12.6 months. HPV positivity was a significant predictor of overall survival (13.6 vs. 6.88 months, $p = 0.024$), while smoking status did not significantly impact overall survival ($p = 0.707$).

Conclusion: HPV status remains a significant predictor of overall survival in the re-irradiation setting with HPV positive rHNC demonstrating superior overall survival following salvage SBRT ± cetuximab.

Introduction

Changes in oropharyngeal squamous cell carcinoma (OPSCC) over the past two decades has been marked by changing patient demographics such as decreased rates of smoking and the emergence of human papilloma virus (HPV). HPV is responsible for an oncologic epidemic: [1] over 60% of OPSCC was estimated to be secondary to HPV in the 2010s versus 16% in the 1980s [2]. OPSCC associated with HPV positivity has a distinct, favorable, prognosis following primary chemoradiotherapy; HPV positivity is the single strongest prognostic factor for OPSCC [3,4]. Similarly, smoking status is known to be an independent risk factor for the development of OPSCC; HPV positivity in the setting of at least 10 pack-year smoking history behaves prognostically as an intermediate risk group [4]. Recently, a retrospective analysis from 2 contemporary RTOG trials examining cisplatin-based chemoradiotherapy and/or cetuximab (RTOG 0129 and 0522) showed that HPV status remains a strong prognostic factor in patients that fail primary chemoradiotherapy with a 2-year overall survival of 55% for HPV+ versus 28% for HPV−, ($p < 0.001$); HPV status was also a significant predictive factor in patients treated with and without salvage surgery [5,6].

At our institution, the preferred salvage re-irradiation regimen for patients with un resectable, locally-recurrent, previously-irradiated head-and-neck cancer is stereotactic body radiotherapy (SBRT). Initial phase I dose escalation, showed the feasibility and safety of 44 Gy in 5 fractions without any grade 3+ toxicity and a 76% overall response rate [7]. Matched pair-analysis further supported the potential efficacy of SBRT+ cetuximab in the re-irradiation setting, for which the safety of this regimen has been validated in both a phase II trial from our institution as well as in recently reported French multi-institutional data [8,9]. Herein, we present a secondary analysis of patients treated at our institution with salvage SBRT± cetuximab (including patients treated on two prospective clinical trials, UPCI 04-144 and 06-093) examining the

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impact of HPV status in the re-irradiation setting. We hypothesize that HPV status will remain a significant predictor of overall survival following re-irradiation with SBRT. Secondarily, we will examine the influence of HPV positivity on failure patterns and treatment characteristics such as toxicity.

Material and methods

All patients treated at The UPMC Cancer Center with rOPSCC salvaged with SBRT± cetuximab from August 2002 and August 2013 were retrospectively reviewed. Patients excluded from this analysis included those with non-oropharyngeal primaries, those treated with SBRT as a planned boost after definitive radiation therapy, patients who had not received prior irradiation, patients who did not complete >50% of prescribed treatment, and patients with non-squamous cell histologies. Patients were referred to SBRT with or without cetuximab after having been deemed unresectable by a multidisciplinary tumor board. Most patients were determined to be surgically unresectable secondary to the extent of disease precluding reconstruction; less commonly, patients were medically inoperable secondary to comorbidity and/or general deconditioning. Original pathology reports of all primary lesions were reviewed where available. HPV status was determined by immunohistochemistry (IHC) using an antibody against p16. A positive test was defined as intermediate/strong nuclear and cytoplasmic staining in $\geqslant$70% of cells. All patients had no chemotherapy, radiation therapy, or ablative surgery at least 1 month prior to SBRT; and underwent formal restaging evaluation to rule our distant metastases (usually via PET/CT) within 1-month prior to SBRT.

SBRT techniques for target delineation, patient setup, and treatment/delivery have been previously described [7,8,10,11]. Briefly, SBRT planning was CT-based or PET/CT-based with custom thermoplastic mask for immobilization delivered using one of several treatment platforms including Cyberknife™ (Accuracy, Inc., Sunnyvale, CA), Trilogy™, and TrueBeam™ (Varian Medical Systems Inc., Palo Alto, CA). SBRT consisted of 40–50 Gy in 5 fractions depending on treatment volume $\geqslant$ 25 cc, delivered on alternating days over 1–2 weeks. Initially in our dose-escalation experience, planning target volume (PTV) equaled gross tumor volume (GTV) with no expansion margin, however based on recent patterns of failure outcomes analysis, we now incorporate a maximum 5 mm GTV to PTV expansion depending on treatment volume, prior treatment, and proximity to surrounding critical structures [10–12]. Organs-at-risk included the spinal cord in all cases and brainstem as well as the parotids, pharyngeal constrictor muscles, mandible and oral cavity depending on treatment site. Dose limit to the spinal cord was set at 8 Gy with SBRT. Building on promising single-institution and Phase II data, SBRT was combined with concurrent cetuximab administered at 400 mg/m^2 on day −7 then 250 mg/m^2 on day 0 and +8 in select patient including patients treated on our prospective Phase II study SBRT+ concurrent cetuximab (UPCI 06-093) [10–12].

The following primary endpoints were assessed post-SBRT stratified by HPV status and smoking history: re-irradiation interval (measured from the time of initial diagnosis to the initiation of SBRT), locoregional control (LRC, defined as failure within any head-and-neck site including regional nodal failure), overall survival (OS, measured from the date of initiation of SBRT to the date of death or last follow-up) and physician recorded toxicities. Using the Kaplan-Meier method for tumor control and survival, a log-rank test was used to compare the difference in time from diagnosis to initiation of SBRT and OS rates by HPV status and smoking history between groups. SPSS software package version 21.0 was used for statistical computation (SPSS Inc, Chicago, IL).

Results

Results: All patients with rOPSCC

Sixty-nine patients (51 males, 18 females; mean age 64.42 ± 10.15 years) with recurrent, previously-irradiated oropharyngeal squamous cell carcinoma (OPSCC), who were treated with SBRT (Cyberknife = 37, Trilogy-IMRS = 12, Truebeam = 20) were included in this study. The median follow-up of all patients was 9.71 months (<1–53 months). The median follow-up for patients who remained alive at last follow-up (n = 15) was 10.1 months (<1–40 months). Patient, tumor, and treatment characteristics are summarized in Table 1.

Smoking history was available for 95.7% of patients (n = 66). The majority of patients were either current or former smokers by history (n = 51,73.9%). Of these, 13 patients (18.8%) continued to smoke through last follow up visit, 34 patients quit smoking after the diagnosis of OPSCC (49.3%), and post-diagnosis smoking data was either unavailable or conflicting for 22 patients (31.9%).

Overall, 33 patients (47.8%) received concurrent cetuximab with SBRT including patients on our prospective institutional protocol UPCI 06-093. There was no difference in cetuximab use between smoking (50%) and nonsmoking (50%) groups.

The average re-irradiation interval was 41.1 months (1–271 months). Neither smoking history (p = 0.354; 29.0 months vs. 46.5 months) nor HPV positive status (p = 0.709; 32.1 months vs. 39.7 months) were associated with a difference in re-irradiation interval.

The most common sites of failure following re-irradiation with SBRT were metastatic disease (n = 18; 26.1%) and persistent local disease (n = 17; 24.6%). The mean time to recurrence was

Table 1
Baseline patient and treatment characteristics.

Characteristics	*N* (%)
Age, years (mean ± standard deviation)	64.4 ± 10.2
Sex	
Male	18 (26%)
Female	51 (74%)
Smoking status (n = 66, 96%)	
Never – less than 10 pack years	15 (22%)
Greater than 10 pack year	51 (74%)
HPV status (n = 30, 43%)	
Positive	17 (57%)
Negative	13 (45%)
Primary site in oropharynx	
Tonsil	26 (38%)
Base of tongue	32 (46%)
Other or NOS	11 (16%)
Prior treatment	
Prior full dose radiotherapy	69 (100%)
Prior surgery	18 (26%)
Prior chemotherapy	44 (64%)
Recurrence treatment site	
Base of tongue	23 (33%)
Cervical lymph nodes	10 (15%)
Base of skull	6 (9%)
Other[a]	30 (43%)
Second primary[b]	14 (20%)
SBRT treatment volume, cc, mean (range)	45 (2.5–345.1)
SBRT Dose, Gy, mean (range)	40.9 Gy (15–50)

[a] Other sites: tonsil, hypopharynx, nasopharynx, parotid, other oropharynx.
[b] Fourteen patients (20.3%) had been previously diagnosed and treated with squamous cell carcinoma of the head and neck and presented with OPSCC as a second primary lesion. Of these, 5 patients were treated for laryngeal squamous cell carcinoma (SCC), 3 patients were treated for oral cavity SCC, and 3 were treated for OPSCC. Thirteen (92.9%) of the patients with second primary tumors were smokers, for the remaining 1 patient smoking status was unknown.