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It is not just IMRT: Human papillomavirus related oropharynx squamous cell carcinoma is associated with better swallowing outcomes after definitive chemoradiotherapy

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SUMMARY

Objectives: Long term swallowing dysfunction in patients with oropharynx squamous cell carcinoma (OPSCC) treated with concurrent chemoradiation (CRT) is declining. While the use of intensity modulated radiotherapy (IMRT) is commonly believed to be a potential cause, we hypothesize that the increasing incidence of human papillomavirus (HPV) related disease may also favorably impact this outcome.
Materials and methods: We reviewed 130 HPV+ and 17 HPV− patients with stage III–IV OPSCC treated exclusively with conventional 3-field radiotherapy with chemotherapy between 2002 and 2010. The rates of normal diet, limited diet (significant restrictions in the types of foods eaten, and/or requiring nutritional supplementation for weight maintenance) and feeding tube dependence (FTD) were compared between HPV+ and HPV− patients. Cox proportional hazards modeling were used to perform univariate analysis (UVA) to examine predictors of a combined endpoint of dietary limitation, which included limited diet and/or FTD. These outcomes were also compared to our previously reported cohort of OPSCC patients treated between 1989 and 2002 to assess changes in toxicity over time given the changing disease epidemiology, in the setting of identical treatment regimens.
Results: With a median follow-up of 55 months, HPV+ patients more frequently had resumed a normal diet (87% vs. 65%) at last follow up and had lower rates of limited diet (9% vs. 18%) and FTD (4% vs. 18%) compared to HPV− patients ($p = 0.02$). HPV status was the only significant predictor of reduced swallowing dysfunction on UVA (HR 0.19; $p = 0.008$). When compared to our 1989–2002 cohort, patients treated between 2002 and 2010 had less FTD (7.5% vs. 34%, $p < 0.001$) and dietary limitations (26% vs.46%, $p < 0.001$) at 6 months post treatment.
Conclusions: HPV+ patients with OPSCC have reduced late swallowing dysfunction after chemoradiation compared to HPV− patients. The changing epidemiology of OPSCC may play a role in toxicity reduction in these patients, independent of the increasing use of IMRT.

Introduction

Late swallowing dysfunction is a significant concern for patients with locally advanced OPSCC treated with concurrent chemoradiotherapy [1,2]. However, recent reports have suggested that this problem may be diminishing in frequency [3,4]. The reason for falling late toxicity rates is unclear. Many techniques have been described to reduce the incidence of long term swallowing dysfunction including improved rehabilitative techniques, improved supportive care during treatment, and the decreasing use of prophylactic gastrostomy tubes during treatment [5,6]. One of the most common reasons cited for an improvement in late swallowing dysfunction has been the increasing use of intensity modulated radiation therapy (IMRT), which allows for better avoidance of normal tissues that are critical to swallowing [3,7–9]. However, the recent increased adoption of IMRT during the last decade has

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occurred simultaneously with changing epidemiology of this disease and the increasing incidence of HPV initiated disease, which now accounts for 70–80% of OPSCC in the U.S [10–12].

In this study, we sought to investigate rates of swallowing dysfunction from our single institution experience using concurrent chemotherapy and non-IMRT, 3D conformal radiotherapy techniques (3D-CRT) from 2002–2010 in patients with a known HPV status. We also contrast this experience with a previously reported historical cohort of patients treated similarly by the same physicians between 1989 and 2002 [13]. All patients were treated at our institution by the same physicians and treatment approach with the assumption that the 1989–2002 cohort would include a greater proportion of HPV− disease consistent with well documented epidemiological trends [11–14]. We hypothesize that rates of swallowing dysfunction in our practice have improved over time independent of IMRT and are lower in the HPV+ cohort.

Materials and methods

We identified patients with histologically confirmed stage III–IVB OPSCC and a known HPV/p16 status treated at our institution between 2002 and 2010, from an IRB approved registry. All patients received definitive 3D-CRT, using traditional 3-field techniques, with concurrent chemotherapy. Patients who demonstrated diffuse and strong staining for p16 on immunohistochemistry, and/or HPV DNA staining on in situ hybridization, were considered HPV+. Patients who experienced a locoregional or distant recurrence and those with less than two years of follow-up were excluded in order to allow for consistent late toxicity assessments. This selection criteria is consistent with other large reports on long term severe toxicity after chemoradiation [15].

Radiotherapy was delivered with once-daily fractions of 2 Gy/fx to a total dose of 70–74 Gy or in twice-daily fractions of 1.2 Gy/fx to a total dose of 74.4 Gy. Twice daily radiation was typically reserved for high functioning patients with T3 or T4 disease. Patients included in this study were treated before our institution transitioned to the use of intensity modulated radiation therapy (IMRT) and a more conventional 3-field approach was utilized. All patients received chemotherapy. Patient treated in our 1989–2002 cohort and the earlier years of the 2002–2010 cohort were typically given 2 courses of 4-day infusions of fluorouracil (1000 mg/m^2/day) and cisplatin (20 mg/m^2/day) during the first and fourth weeks of radiation, as per our previous institutional standard [16]. In recent years, single agent high dose cisplatin (100 mg/m2) on days 1, 22 and 43 of the radiation has more frequently been used. 3 HPV+ patients and 1 HPV− patient was treated with concurrent cetuximab. All patients treated in both the 1989–2002 and 2002–2010 cohorts were treated by a single radiation oncologist (JPS). Salvage neck dissection was reserved for patients with clinically, radiographically or metabolically persistent neck disease three months after the completion of therapy.

Long term swallowing dysfunction was serially assessed during routine multispecialty evaluation at 3, 6, 12, and 24 months post CRT. Patients were categorized as having one of three possible long term swallowing outcomes: (1) feeding tube dependence (FTD), (2) limited diet, defined as patients requiring nutritional supplements for weight maintenance, or having significant limitations in the types of foods eaten; (3) normal diet, defined as the ability to eat a complete diet similar to the pretreatment diet, independent of the need for supplementation. These measures were chosen to correspond with the swallowing outcomes assessed in our historical cohort, thus allowing for consistent comparison between the groups.

The primary analysis compared swallowing outcomes within the 2002–2010 cohort between patients with HPV+ and HPV− disease. For our secondary analysis, we compared long term swallowing outcomes in our 2002–2010 cohort with our previously reported 1989–2002 cohort [13]. We selected only the OPSCC patients out of the historical cohort (97/196 patients) to allow for a proper disease site specific comparison. Baseline demographics and swallowing function in the HPV+ vs. HPV− groups were compared using the Chi-square test or Fisher's exact test (categorical variables) or Wilcoxon rank sum test (continuous variables). Cox proportional hazards modeling were used to perform univariate analysis (UVA) to examine predictors of dietary limitation at 2 years, which included a combined endpoint of either limited diet and/or feeding tube dependency. Multivariate analysis could not be done due to an insufficient number of events. FTD and limited diet were compared between the 1989–2002 and 2002–2012 cohorts at similar time points using the Chi-square test or Fisher's exact test. Analyses were done using SAS software version 9.1 (SAS Institute, Inc., Cary NC, USA). All statistical tests were two-sided, and $p < 0.05$ was used to indicate statistical significance.

Results

A total of a 147 patients (130 HPV+, 17 HPV−) comprised the 2002–2010 cohort for the first part of this study. Baseline patient and treatment characteristics are detailed in Table 1. The median follow-up was 55 months (range, 12–132). HPV+ patients tended to be younger, have a better Karnofsky Performance Status (KPS), and were more likely to be never smokers. Patients with HPV− tumors were more likely to present with advanced T stage compared with patients with HPV+ tumors, while higher nodal stage was more common in the HPV+ group. More HPV+ patients received daily (QD) vs. twice daily (BID) radiation. Chemotherapy regimens were similar in the HPV+ and HPV− patients. Rates of limited diet and FTD at 3, 6, 12, 24 months post treatment are shown in Table 2. At 2 years, HPV+ patients experienced a lower incidence of limited diet (8.6% vs. 33.3%, $p = 0.014$) and FTD (1.6% vs. 12.5%, $p = 0.06$) compared to HPV− patients. With a median follow-up of 55 months, HPV+ patients more frequently had resumed a normal diet (87% vs. 65%) at last follow up and had lower rates of limited diet (9% vs. 18%) and FTD (4% vs. 18%) compared to HPV− patients ($p = 0.02$) (Fig. 1).

UVA analysis found that HPV+ status as the only factor significantly associated with a reduced risk of a combined swallowing dysfunction endpoint that included feeding tube dependence or a limited diet at 2 year follow up (HR 0.19; $p = 0.008$). While a greater than 10 pack-year smoking history trended toward significance (HR 3.53; $p = 0.06$), performance status, stage, T and N descriptors, comorbidities, type of chemotherapy, radiation schedule, and lymph node dissection were not significantly associated with long term swallowing dysfunction (Table 3).

In our second analysis, we compared rates of dietary limitation and FTD in our current cohort of 147 pts treated between 2002 and 2010 cohort to a cohort of 97 pts treated between 1989 and 2002 cohort. At 6 months post-treatment, patients in the 2002–2010 cohort had lower rates of limited diet (25.9% vs.45.7%; $p = 0.001$) and FTD (7.5% vs.34%; $p < 0.001$) than those in the 1989–2002 cohort. These differences were most pronounced within the first year post treatment, and were no longer significant 2 years post treatment (Table 4).

Discussion

This study sought to understand whether HPV+ patients experience more favorable long term swallowing outcomes than HPV− patients controlling for radiation therapy planning by excluding the impact of IMRT. We found in our initial direct