The Laryngoscope

Case Report

Delayed Lower Cranial Neuropathies Following Primary Radiotherapy for Oropharyngeal Squamous Cell Carcinoma

Andrew T. Huang, MD; Shiyu Song, MD; Laura M. Dominguez, MD; Josephine Nguyen, MD; Richard A. Goldman, MD; Evan R. Reiter, MD FACS

Objectives/Hypothesis: Delayed lower cranial neuropathy is a rare complication following primary radiotherapy for head and neck cancer, and has been most associated with nasopharyngeal carcinoma with minimal data regarding this outcome in the treatment of the oropharynx. No reports, to the authors' knowledge, have described this complication following intensity modulated radiation therapy (IMRT) for oropharyngeal primaries. Once encountered, this adverse outcome can have serious impacts on speech and swallowing. We present here our institution's experience with delayed cranial neuropathies following primary radiation therapy for oropharyngeal squamous cell carcinoma, as well as document the only reported case following IMRT.

Key Words: Oropharyngeal cancer; radiation; cranial neuropathy; intensity modulated radiation therapy.

***Laryngoscope*, 123:1207–1209, 2013**

INTRODUCTION

The use of primary chemoradiotherapy as an organ-sparing and less invasive treatment for head and neck squamous cell carcinoma (HNSCC) is well-established.[1,2] However, as the incidence of human papilloma virus (HPV)-associated HNSCC increases, the treatment regimens and available modalities, especially in the oropharynx, have expanded significantly. Specifically, advances in endoscopic and transoral robotic surgery (TORS) have revolutionized the way oropharyngeal cancers can be addressed and managed.

Due to the relative radiosensitivity of poorly differentiated early-stage oropharyngeal cancers, several studies regarding primary radiotherapy have revealed long-term survival of up to 91%.[2,3] Although the morbidity of radiation therapy for HNSCC, including mucositis, xerostomia, and dysgeusia, are well known, cranial neuropathy is an uncommon complication; therefore, it is infrequently reported. When encountered, however, palsies of lower cranial nerves (CN) can severely impact quality of life, and they usually require intervention due to associated deficits in swallow, speech, shoulder function, and voice. Much of the literature on radiation-induced cranial nerve palsies has been extrapolated from data on nasopharyngeal carcinoma, and little has been reported on this complication in the treatment of the oropharynx. No reports, to the authors' knowledge, have described this complication following intensity modulated radiation therapy (IMRT) for oropharyngeal HNSCC. We present three patients with delayed onset palsies of cranial nerves X, XI, and XII following primary radiotherapy, using both 3D conformal radiation therapy (3DRT) and IMRT for oropharyngeal HNSCC.

Case Presentation 1

A 45-year-old male with T2N0M0 squamous cell carcinoma of the left tonsil was treated with primary radiotherapy in February 2004, delivered using 3DRT, initially with bilateral opposed fields to 39.6 Gy at 1.8 Gy per fraction, followed by off-cord boost to the anterior neck and electron boost to the posterior neck to 54 Gy. The left oropharynx and pharyngeal space were treated to 71.4 Gy with opposed oblique fields. The radiation dose was prescribed to 92%, with a hot spot of nearly 6% to the left oropharynx. The patient then returned to the head and neck tumor clinic 5 years after treatment conclusion, with new onset hoarseness and left shoulder weakness. Clinical evaluation demonstrated atrophy of the left trapezius muscle, left true vocal cord paralysis, and left hemitongue fasciculations with leftward deviation on protrusion. Workup including brain MRI, as well as neck and chest computed tomography (CT) scans, failed to reveal any evidence of ischemic injury, brainstem lesions, or recurrent or metastatic disease. Due to persistent vocal cord dysfunction as well as trace

From the Department of Otolaryngology–Head and Neck Surgery (A.T.H., L.M.D., J.N., R.A.G., E.R.R.) and the Department of Radiation Oncology (S.S.), Virginia Commonwealth University, Richmond, Virginia; the Department of Head and Neck Surgery (A.T.H.), The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

Editor's Note: This Manuscript was accepted for publication November 19, 2012.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Andrew Huang, Department of Otolaryngology–Head and Neck Surgery, Virginia Commonwealth University, Richmond, VA, 23298-0614. E-mail: athuang@mdanderson.org

DOI: 10.1002/lary.23938

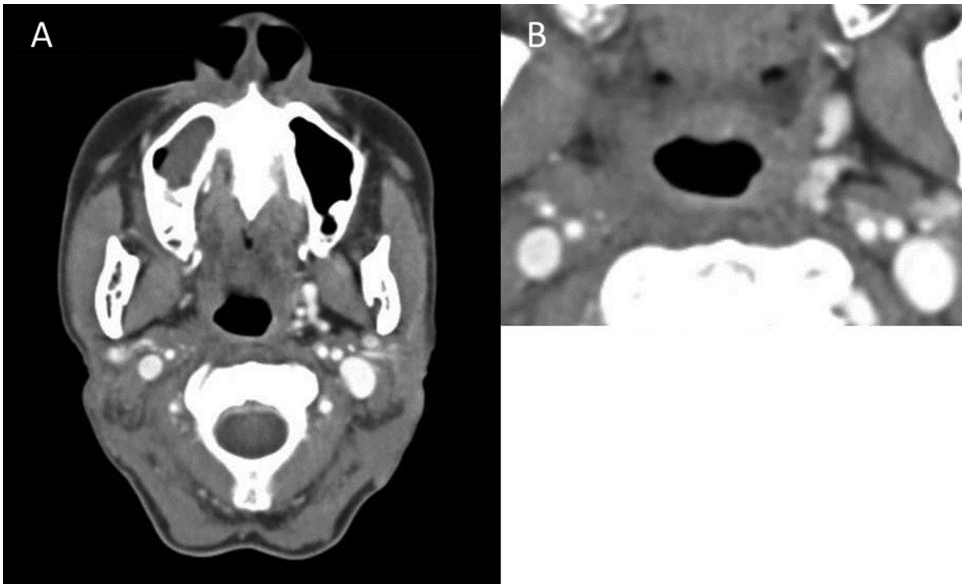

Fig. 1. Post-treatment CT scan of patient 2: (A) Representative image from axial CT scan demonstrating decreased parapharyngeal fat and obliteration of vasculature. (B) Enlargement of parapharyngeal spaces. Note asymmetry in parapharyngeal fat and vascular pattern.

aspiration, injection laryngoplasty was performed. Failure of symptoms to improve over 12 months following injection prompted left medialization laryngoplasty. The patient currently remains disease-free.

Case Presentation 2

A 60-year-old female with T3N2bM0 squamous cell carcinoma of the right tonsil was treated with primary chemoradiotherapy completed in April 2005. Her treatment was delivered using IMRT, with a prescribed dose of 69.93 Gy to the gross tumor volume (GTV) at 2.1 Gy per fraction, 60 Gy to the clinical target volume potentially containing microscopic disease at 1.8 Gy per fraction, and 54 Gy to the uninvolved neck at 1.6 Gy per fraction. The maximal dose (Dmax) was 75.88 Gy located in the right oropharynx. On routine cancer surveillance 3 years following treatment conclusion, the patient reported new-onset dysphonia. Clinical examination revealed right true vocal cord paralysis. Although the patient's voice quality was subjectively bothersome, she failed to demonstrate aspiration and refused elective intervention. Complete head and neck examination, as well as CT scans of the neck (Fig. 1) and chest failed to demonstrate recurrent locoregional disease or distant metastases. One year after discovery of vocal cord dysfunction, the patient presented with progressive right tongue weakness. Oral inspection demonstrated right tongue atrophy with rightward deviation on protrusion, as well as asymmetric palatal elevation. Magnetic resonance imaging (MRI) of the brain and neck revealed no significant findings. The patient continues on close follow-up, without improvement in cranial neuropathies and without evidence of recurrent disease.

Case Presentation 3

A 56-year-old male with a history of T1N2bM0 squamous cell carcinoma of the left tonsil, who was treated with primary chemoradiation therapy ending October 2000, presented urgently to the head and neck tumor clinic nearly 6 years after treatment conclusion secondary to increasing hoarseness. Review of the patient's treatment history revealed that he was treated with 3DRT at 1.8 Gy per fraction, initially with opposed bilateral fields to 39.6 Gy, followed by an off-cord boost to 50.4 Gy. An anterior field to treat the supraclavicular regions bilaterally was used to deliver 50.4 Gy. He was further treated to 60.4 Gy at 2 Gy per fraction using off-cord fields to the anterior neck and electron fields to the posterior neck. Finally, he received 10 Gy in 5 fractions to the left tonsillar region for a total of 70.4 Gy, using oblique wedged pairs plus a lightly weighted right lateral field. Clinical examination revealed a new left true vocal cord hypomobility, prompting a workup including CT scans of the neck and chest that failed to demonstrate significant pathology. Three months later, the patient again presented urgently due to new onset stridor. Bilateral true vocal cord immobility was observed, and the patient required tracheotomy. Three years following tracheostomy, 9 years after the end of radiation, the patient reported new onset dysarthria. Left hemitongue fasciculations were evident, which progressed to bilateral complete tongue immobility. MRI scans of the brain and neck failed to reveal any definitive pathology. Due to aspiration and inability to swallow, the patient had a gastrostomy tube placed. He is currently tracheostomy and gastrostomy-dependent.

DISCUSSION

Neuropathies following HNSCC irradiation have been estimated to range from 1% to 5%,[4] but have generally only been observed following treatment of nasopharyngeal carcinoma due to its proximity to the skull base and brainstem. Although considered radioresistant, peripheral nerves have been shown to exhibit fibrosis and Wallerian degeneration following radiation exposure.[5] Injury to lower cranial nerves is thought to be mediated by this primary radiation-induced damage, or also

secondary to progressive fibrosis of the soft tissues adjacent to the nerves, resulting in delayed injury to the neural vascular supply. In fact, MRI findings in patients receiving 60 to 70 Gy to the pharynx have demonstrated evidence of retropharyngeal and parapharyngeal space thickening in 93% of cases.[6] Lin et al.,[4] in a review of 1,200 patients with nasopharyngeal carcinoma treated with radiation therapy, identified 19 patients with delayed cranial nerve palsies. The hypoglossal nerve was the most commonly affected, followed by the vagus nerve and the spinal accessory nerve. It is unclear why the hypoglossal nerve is so susceptible to injury, but there have been reports of hypoglossal nerve palsy following laryngeal mask airway pressure-induced injury. Just as an external device can relay hypoglossal injury, it can be hypothesized that the nerve's close course to the tongue base predisposes it to radiation damage, either by direct fibrosis or vascular injury; whereas the vagus nerve benefits from a medial course in the vascular sheath, and the spinal accessory nerve is protected by a lateral course and separate cervical rootlet contributions.[7] The time to presentation of nerve palsies has been reported to range anywhere between 12 to 240 months after radiation exposure[4,8–10]

With the incidence of oropharyngeal HNSCC increasing secondary to HPV prevalence, the outcomes of uni- and multimodality therapy are being critically evaluated. It is generally recognized that early stage, and even less bulky oropharyngeal cancers with minimal nodal metastases, can be treated primarily with radiotherapy or surgery.[3] Although it is a relatively new option, TORS has offered a less invasive approach to the oropharynx without sacrificing visualization or oncologic safety. In a recent review of 31 patients with oropharyngeal HNSCC undergoing TORS, Weinstein et al.[11] demonstrated that 86% and 30% of patients with N1 and N2 disease, respectively, were spared the need for adjuvant chemotherapy, and that 29% of N1 patients did not require adjuvant radiation based on final pathologic analysis. The ability to avoid or even deintensify radiation in this setting may prevent of late radiation complications such as cranial nerve palsy. Although IMRT has largely supplanted 3DRT in the management of head and neck cancer due to its more specific application and fewer complications, this series, the first to the authors' knowledge, demonstrates that it still can result in delayed lower cranial neuropathies.

CONCLUSION

Cranial nerve dysfunction following head and neck irradiation is a complex problem. Further research is warranted in investigating possible risk factors that may predispose these patients to nerve injury. Although the average time to presentation of cranial nerve palsies can be delayed to as much as 112 months, recurrent, second primary, or distant metastatic disease must always be considered and ruled out. Symptomatic treatment should then be pursued, if needed, as the most common nerves involved (hypoglossal, vagus, spinal accessory) are intimately involved in quality of life, and in the vital functions of speech articulation, swallowing, and phonation.

BIBLIOGRAPHY

1. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *NEJM* 2003;349:2091–2098.
2. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J RadiatOncolBiol Phys* 2010;76:1333–1338.
3. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? *JNCCN* 2011;9:665–673.
4. Lin YS, Jen YM, Lin JC. Radiation-related cranial nerve palsy in patients with nasopharyngeal carcinoma. *Cancer* 2002;95:404–409.
5. Shapiro BE, Rordorf G, Schwamm L, Preston DC. Delayed radiation-induced bulbar palsy. *Neurology* 1996;46:1604–1606.
6. Nomayr A, Lell M, Sweeney R, Bautz W, Lukas P. MRI appearance of radiation-induced changes of normal cervical tissues. *EurRadiol* 2001;11:1807–1817.
7. Stewart A, Lindsay WA. Bilateral hypoglossal nerve injury following the use of the laryngeal mask airway. *Anaesthesia* 2002;57:264–265.
8. Berger PS, Bataini JP. Radiation-induced cranial nerve palsy. *Cancer.* 1977;40:152–155.
9. Cheng VST, Schulz MD. Unilateral hypoglossal nerve atrophy as a late complication of radiation therapy of head and neck carcinoma: a report of four cases and a review of the literature on peripheral and cranial nerve damages after radiation therapy. *Cancer* 1975;35:1537–1544.
10. King AD, Ahuja A, Leung SF, Chan YL, Lam WWM, Metreweli C. MR features of the denervated tongue in radiation induced neuropathy. *Br J Radiol* 1999;72:349–353.
11. Weinstein GS, Quon H, O'Malley BW, Kim GG, Cohen MA. Selective neck dissection and deintensified postoperative radiation and chemotherapy for oropharyngeal cancer: a subset analysis of the University of Pennsylvania transoral robotic surgery. *Laryngoscope* 2010;120:1749–1755.