Vocal Fold Paralysis as a Delayed Consequence of Neck and Chest Radiotherapy

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Abstract

Objective. To describe a series of cases of vocal fold paralysis years after radiation therapy, including presentation, clinical course, and treatment.

Study Design. Case series with chart review.

Setting. Tertiary care center.

Subjects and Methods. A review of 8 years of patient records yielded 10 patients (8 male and 2 female; average age 57 years [range, 29-76 years]) with vocal fold paralysis and a history of radiation therapy to the head, neck, or mediastinum. These patients did not have other possible etiologies of vocal fold paralysis. Demographic, diagnostic, clinical course, and treatment data were collected.

Results. On average, 21 years (range, 1-27 years) elapsed between completion of radiation and presentation with vocal fold paralysis. Original pathologies included Hodgkin lymphoma (5), squamous cell carcinoma of the head and neck (4), and peripheral T-cell lymphoma (1). Eight patients had unilateral left vocal fold paralysis, and 2 had bilateral neuropathy; none recovered spontaneously. All patients had dysphonia, and nearly all patients also complained of dysphagia. Six elected not to be treated. Four underwent injection augmentation with resolution of voice complaints.

Conclusions. Radiation therapy has the potential to cause laryngeal neuropathy years to decades after treatment. The potential for recovery is low, but injection augmentation can relieve symptoms. Development of contralateral neuropathy and altered tissue response are considerations in treatment.

Keywords
radiation therapy, vocal fold paralysis, laryngeal neuropathy, vocal fold injection, delayed cranial neuropathy

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Radiation therapy to the larynx and pharynx is well known to cause direct laryngeal tissue injury, especially when the larynx, pharynx, and oropharynx are treated for locally advanced head and neck cancer.1 When new laryngeal findings appear well after the end of radiation, the relationship may be less apparent, particularly if the larynx itself was not in the radiated field. Vocal fold paralysis (VFP) has been sparsely reported in this context. Consequently, such a finding raises questions regarding cause. Recurrent or second primary disease is always the principal concern, but the possibility of radiation-induced damage should be considered in its absence.

In peripheral nerves, radiation-induced nerve damage occurs in a delayed fashion after local radiation exposure. Radiation fibrosis progresses through 3 stages: a prefibrotic phase largely involving endothelial cells, a fibrotic phase with fibroblast deregulation and active matrix deposition, and a late fibrotic-atrophic phase with retractive fibrosis and apoptosis.2 Free radical species, especially reactive oxygen species, are thought to promote fibrogenesis when mechanisms for their disposal are overwhelmed, a condition that persists in the setting of chronic inflammation or hypoxia.2 Nerve damage results from a combination of direct axonal injury and demyelination, indirect connective tissue damage around nerves, and ischemia due to interruption of local capillaries.3 This damage accumulates to produce symptoms of neuropathy over the course of years.

Radiation neuropathy is generally considered progressive and irreversible, occurring at least months to years after cessation of therapy,4 with latency inversely related to radiation dose.4,5 Therapeutic risk factors include total radiation dose and large dose per fractionation, as well as combination with other modalities such as surgery and chemotherapy.6,7 Patient-related risk factors include age, obesity, comorbid health conditions, and preexisting neuropathies.2 Symptomatic neuropathy increases in incidence with time after treatment (a survival
disadvantage) and can significantly affect patients’ quality of life. The purpose of this article is to report our experience with a group of patients, including 5 patients with Hodgkin lymphoma who developed delayed unilateral and bilateral VFP years after radiation therapy for the purpose of clarifying these clinically important issues.

Methods
This study was approved by the Institutional Review Board of Weill Cornell Medical College. Patients were identified through a review of the senior author’s medical records from 2005 to 2013. Information extracted from the medical record included the original malignancy for which radiotherapy was used, types of therapy, age at diagnosis of VFP, latency from treatment to vocal symptoms, other associated symptoms, medications, comorbidities, treatment, follow-up, and outcomes. Subjects were excluded if any other etiology of VFP (other than idiopathic) was considered possible.

Results
Ten patients, 8 male and 2 female, presented with VFP after radiotherapy. Age of onset of voice complaints ranged from 29 to 76 years, with an average of 57 years. Clinical assessment was based principally on videostrobolaryngoscopy. Each patient underwent radiologic investigation of the course of the affected nerve(s) as would be performed for any patient with unexplained VFP. This typically comprised a contrasted computed tomography (CT) of the neck extending through the aortic arch, although several underwent additional positron emission tomography (PET) and magnetic resonance imaging (MRI). Symptoms arose 1 to 27 years after radiation therapy to head, neck, and/or mediastinum (Table 1). Due to the latency of VFP after treatment, the dose and fractionation schedules for most patients were not available. All patients presented with the complaint of dysphonia, while half also acknowledged fatigue or shortness of breath while speaking. Nine patients complained of dysphagia to solids, liquids, or both, while 4 complained of globus, 2 of cough, and 1 of throat pain. Seven patients, including all 5 patients with Hodgkin lymphoma, had hypothyroidism. Other comorbidities included hypertension, diabetes, Crohn’s disease, coronary artery disease or cardiomyopathy, and gastroesophageal reflux disease or peptic ulcer disease. No patients spontaneously recovered vocal fold motion. Our patients were followed for an average of 13.5 months (range, 3 months to 2 years). Four patients underwent unilateral injection augmentation, one on 2 occasions, achieving amelioration of their symptoms.

Discussion
Peripheral nerves have traditionally been considered relatively radiation resistant, but cases of delayed radiation-induced peripheral neuropathy have appeared in the literature since 1966. Most cranial neuropathies occur after skull base or neck irradiation, with the optic and hypoglossal nerves proving most susceptible. The range in percentage of patients affected with delayed radiation-induced cranial neuropathy extends to one-third in some series.

Recurrent laryngeal neuropathy following radiation is much more rarely reported but can occur after skull base, neck, or mediastinal radiation. Of 150 breast cancer survivors who received mediastinal radiation without neoadjuvant or concurrent chemotherapy in the 1960s, 12 developed VFP over 2 to 25 years, 11 on the left. Earlier presentation with VFP was correlated with the combined use of 3-field electron and photon treatment (at a rate of 10%). Patients with lower radiation dosage and smaller field developed left VFP at a rate of 5% with greater than 20 years of latency to presentation. None of these patients recovered nerve function. There are also several reports of recurrent laryngeal neuropathy secondary to radiation for nasopharyngeal carcinoma (NPC). This skull base radiation is typically associated with multiple cranial neuropathies and bilateral laryngeal involvement. Latency to symptomatic neuropathy is reported to range from 1 to 34 years. In patients who were followed for 20 years after NPC radiation, 44% developed some cranial neuropathy, and there are no reports of nerve recovery. In the few cases of VFP following radioactive iodine for treatment of thyroid pathology, onset occurred 3 to 7 days after treatment without any observed nerve recovery, implicating a different pathophysiologic process such as acute edema in the nerve damage. There is only 1 previously reported case of left recurrent laryngeal nerve (RLN) paralysis 22 years after mantle radiation for Hodgkin lymphoma.

The patients in our cohort developed VFP years to decades after completing radiotherapy, a range consistent with the cases reported above. Short of biopsy, it is never certain whether a unilateral RLN palsy can be definitely attributed to remote radiation, but in our patients, the exclusion of other factors by history and radiographic examination makes the relationship highly likely. Although the incidence of idiopathic VFP has not been definitively established for any population, it is not a common neuropathy, and the probability that the cases in our series, each with specific and similar histories, may be explained on that basis seems diminishingly small.

The left RLN is more likely to sustain radiation-induced damage sufficient to produce VFP than its right-sided counterpart. All of our patients demonstrated left-sided VFP, and 2 had evidence of bilateral neuropathy on stroboscopy. Five cases resulted after significant mediastinal radiation; in 2 patients, a second left-sided cranial neuropathy developed, implicating what was likely a high radiation dose at the skull base on that side; another 3 patients underwent radiation for left-sided primary tumors. Predominant left-sided involvement in the other 2 cases (patients 1 and 3) could be due to the nerve’s length and/or a variable susceptibility to radiation-induced damage. If radiation and its resulting local hypovascularity, fibrosis, and contracture provide a “first hit,” increasing vulnerability to viral-associated or idiopathic neuropathy, greater nerve length and exposure could account for left-sided predisposition.
As in other reports, all of our patients presented with varying degrees of hoarseness, found to be secondary to VFP. Most also complained of chronic cough, globus sensation, or throat pain. Although 9 patients reported some degree of dysphagia, one serious enough to require gastrostomy tube feedings, it is impossible to ascribe this trend simply to VFP. Dysphagia could result from soft tissue post-radiation fibrosis or esophageal stricture, common sequelae of radiation and even more commonly chemoradiation, or due to the presence of a concurrent sensory neuropathy. There are very few reports of sensory deficits in the cranial nerves as a result of radiation therapy, although it probably occurs. In one study, electromyography detected abnormalities in both the superior and recurrent nerves of 2 of 3 patients who developed the bilateral deficits. All of these patients also developed the primary tumor.11 In our study, 2 of the patients with Hodgkin lymphoma received chemotherapy while 3 did not, but their latency to VFP was essentially the same. Whether the addition of chemotherapy enhances or accelerates this process has yet to be conclusively ascertained, but it was not demonstrated in our series.

Chemotherapeutic agents are also known to cause neuropathy. Their addition to the treatment regimens of our patients could have influenced the development of their motor neuropathy. However, most classes of agents induce predominantly sensory neuropathies. These usually begin during treatment and persist for only months after treatment.20 Motor disturbances are rarer, associated largely with the vinca alkaloids, and they also appear to improve and usually resolve with time.21 At least 40 cases of adult and pediatric RLN neuropathy have been reported as a result of vinca alkaloid therapy. In all of these cases, paresis was apparent almost immediately, and vocal fold function recovered with cessation of treatment or reduction in dose.22-26 There are no reports of chemotherapy inducing a delayed RLN paralysis, as there are for radiation-induced neuropathy.6 Chemotherapy and radiation affect nerves by different means.

Chemotherapy is known to increase the toxicity of radiation, and it is possible that it contributed to establishing the ongoing fibrosis seen in our patients, especially their dysphagia. However, radiation alone may establish ongoing fibrosis with resultant RLN neuropathy.11 Few prospective studies measuring the development of radiation neuropathy have been completed, none documenting RLN neuropathy and none without confounders, including chemotherapy and surgery. However, 1 prospective study linked total dose of radiation alone with the development of delayed brachial plexus neuropathy at an overall incidence of 14%.5 In a large cohort of patients who developed VFP after mediastinal radiation, none received chemotherapy for their primary tumor.11 In our study, 2 of the patients with Hodgkin lymphoma received chemotherapy while 3 did not, but their latency to VFP was essentially the same. Whether the addition of chemotherapy enhances or accelerates this process has yet to be conclusively ascertained, but it was not demonstrated in our series.

The cohort of 5 patients with Hodgkin lymphoma in this study represents the largest reported group of patients with delayed VFP after mantle radiation and is remarkably homogeneous. Although specific treatment schedules were unavailable for all patients, they all received mantle radiation between 1985 and 1987 and developed dysphonia secondary to VFP 20 to 27 years later, with 2 developing bilateral deficits. All of these patients also developed the anticipated hypothyroidism, and 3 developed significant cardiovascular disease. It is important to consider RLN neuropathy as a delayed side effect of radiation in these patients.

Since patients do not generally recover nerve function after radiation-induced injury, treatment is an immediate consideration, based on patient symptoms. No patients in this series recovered during our surveillance period (3-24+ months). Four patients with unilateral VFP underwent injection augmentation. Results were satisfactory in all patients, and 1 patient returned for a second injection after the injectable was resorbed. Patients who did not undergo injections

### Table 1. Summary of Cases.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Tumor</th>
<th>Oncologic Treatment</th>
<th>Years to PX</th>
<th>Cranial Neuropathy</th>
<th>Treatment of VFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>73/M</td>
<td>T4N2 NPC</td>
<td>Chemo/rads</td>
<td>12</td>
<td>Left VFP</td>
<td>Left IA ×2</td>
</tr>
<tr>
<td>P2</td>
<td>78/M</td>
<td>Left BOT SCC</td>
<td>Chemo/rads</td>
<td>1</td>
<td>Left VFP</td>
<td>Left IA</td>
</tr>
<tr>
<td>P3</td>
<td>30/M</td>
<td>CD3+ peripheral T-cell lymphoma (Stage 1e)</td>
<td>Chemo/rads, stem cell transplant</td>
<td>5</td>
<td>Left VFP</td>
<td>Left IA</td>
</tr>
<tr>
<td>P4</td>
<td>63/M</td>
<td>T4aN2bM0 BOT SCC</td>
<td>Chemo/rads</td>
<td>7</td>
<td>Left VFP, left CN</td>
<td>X</td>
</tr>
<tr>
<td>P5</td>
<td>61/F</td>
<td>T1N2bM0 left tonsil SCC</td>
<td>Chemo/rads</td>
<td>3</td>
<td>Left VFP, left CN</td>
<td>XII paresis</td>
</tr>
<tr>
<td>P6</td>
<td>70/F</td>
<td>Hodgkin lymphoma</td>
<td>Radiation</td>
<td>27</td>
<td>Left VFP</td>
<td>X</td>
</tr>
<tr>
<td>P7</td>
<td>68/M</td>
<td>Hodgkin lymphoma</td>
<td>Chemo/rads</td>
<td>20</td>
<td>Bilateral VFP</td>
<td>X</td>
</tr>
<tr>
<td>P8</td>
<td>41/M</td>
<td>Hodgkin lymphoma</td>
<td>Radiation</td>
<td>25</td>
<td>Left VFP</td>
<td>X</td>
</tr>
<tr>
<td>P9</td>
<td>44/M</td>
<td>Hodgkin lymphoma</td>
<td>Chemo/rads</td>
<td>25</td>
<td>Left VFP</td>
<td>X</td>
</tr>
<tr>
<td>P10</td>
<td>56/M</td>
<td>Hodgkin lymphoma</td>
<td>Radiation</td>
<td>25</td>
<td>Bilateral VFP</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: BOT, base of tongue; CN, cranial nerve; IA, injection augmentation; NPC, nasopharyngeal carcinoma; PX, presentation; Chemo/rads, combination chemotherapy and radiation therapy; SCC, squamous cell carcinoma; VFP, vocal fold paralysis.
either had airway permissive bilateral neuropathy or determined that their dysphonia was not significant enough to warrant a procedure. Permanent medialization is a consideration, but the possibility of future contralateral neuropathy must be considered. Reports of tracheostomy for radiation-induced bilateral RLN palsies are present in the literature.\textsuperscript{10,12,13} Sixty percent of patients who developed 1 cranial neuropathy after radiation for NPC developed another within 6 months.\textsuperscript{8} Electromyography studies in 3 patients with unilateral radiation-induced VFP demonstrated contralateral subclinical abnormalities in 2.\textsuperscript{19} On the other hand, 7 patients with RLN palsy were treated with laryngoplasty in 1 report, and no subsequent airway problems were reported during an undisclosed period of observation.\textsuperscript{12} When such patients undergo framework surgery, some patient education and long-term postoperative monitoring may be prudent.

This study group serves to emphasize the importance of surveillance for delayed neuropathy as patients survive for longer periods after therapy. Due to the latency of RLN neuropathy, it may not be recognized in patients, adequate treatment may not be applied, and the potential for progression may not be acknowledged. This cohort was not drawn from a prospective longitudinal trial, and thus, no conclusion may be drawn between the treatment modalities and dosages and the rate of RLN neuropathy.

**Conclusion**

Radiation therapy affecting the peripheral course of the RLNs may cause laryngeal neuropathy years to decades after treatment, becoming more problematic as patient survival increases. The detrimental effects of radiation therapy on local peripheral nerves are probably the result of slowly progressive fibrosis and hypoxemia due to compromised local circulation. Tumor recurrence and second primaries must be excluded in the workup of new neuropathy. Although radiation-induced neuropathies are relatively rare, they are usually permanent and significantly affect patient quality of life. Postradiation laryngeal neuropathy is marked by a high incidence of associated dysphagia in addition to dysphonia and has minimal potential for spontaneous recovery. Augmentation or medialization should be undertaken with consideration not only for altered tissue response when the larynx lies in the radiated field but also for the potential of future deficits developing in the contralateral nerve exposed to the same radiation.

**Author Contributions**

Brianna K. Crawley, substantial contributions to conception/design of the work, acquisition, analysis and interpretation of data, drafting and revising the work, final approval, accountability; Lucian Sulica, substantial contributions to conception/design of the work, acquisition, analysis and interpretation of data, drafting and revising the work, final approval, accountability.

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**References**


