Clinical Assessment and Treatment of the Dysfunctional Larynx after Radiation

Clint T. Allen, MD\textsuperscript{1}, Chia-Jung Lee, MD\textsuperscript{2}, and Albert L. Merati, MD\textsuperscript{1}

Abstract

Objective. To review the pathophysiology of early and late radiation-related tissue changes, methods to differentiate these changes from disease recurrence, and treatment of these changes in the irradiated larynx.

Data Sources. Peer-reviewed publications.


Conclusions/Implications for Practice. Early and late radiation-related changes in the larynx manifest variably between individual patients. Severe radiation-related tissue changes in the larynx and recurrent malignancy share many clinical characteristics, and the presence of malignancy must be considered in these patients. Positron emission tomography may help select patients who need operative biopsy to rule out recurrence. In patients with a cancer-free but dysfunctional larynx, both surgical and nonsurgical treatment options, including hyperbaric oxygen, are available for attempted salvage. Further investigation is needed before hyperbaric oxygen can be considered standard-of-care treatment for these patients.

Keywords
larynx, radionecrosis, positron emission tomography, salvage, hyperbaric oxygen treatment

Introduction

Stage I or II laryngeal squamous cell carcinoma (LxSCC) can be treated with single modality radiation therapy (XRT) or surgery with comparable oncologic efficacy.\textsuperscript{1,2} Advanced stage LxSCC is often treated with chemotherapy and radiation (CRT) as an alternative to extirpative surgery with the hope of larynx preservation. Local control of low volume (T1) disease treated with XRT alone is good with recurrence rates of 5% to 10%,\textsuperscript{3} but becomes poor for larger volume disease (T2-T4) treated with XRT or CRT with recurrence rates approaching 50%.\textsuperscript{3-5} Surgical salvage of recurrent LxSCC is achievable with disease-specific survival rates of 50% to 90%.\textsuperscript{3,6,7}

Given the high risk of recurrent disease after XRT for LxSCC, close follow-up after treatment is critical for long-term survival.\textsuperscript{3,8,9} Herein lies a difficult problem for the otolaryngologist: acute and late effects of XRT on the larynx and surrounding tissues complicate efficient cancer surveillance.\textsuperscript{10,11} Signs and symptoms of XRT-related tissue changes can mirror those of recurrent LxSCC. This article reviews the pathophysiology of XRT-associated tissue changes, discusses terminology that has been loosely applied to this clinical problem, evaluates current modalities to help differentiate XRT changes from persistent/residual cancer in the larynx, and summarizes studies evaluating the efficacy of surgical and nonsurgical treatment of XRT-related tissue changes.

Methods

PubMed was used to search for articles related to the topics outlined. For the sections “Pathophysiology of Early and Late XRT-related Tissue Changes,” “Differentiating Late XRT-related Tissue Changes and Tumor Recurrence,” and “Measures of Laryngeal Tumor Recurrence,” search parameters included radiation effects larynx and larynx cancer recurrence radiation and variations of these inputs. For the section “Treatment of XRT-related Tissue Changes,” search inputs included treatment larynx necrosis radiation, treatment chondronecrosis larynx, and hyperbaric oxygen larynx. Articles were reviewed by the authors and were excluded if they were not available in English or, if in the opinion of the authors, they did not contribute meaningfully to the primary discussion points of the article. Results of the search for hyperbaric oxygen larynx yielded 9 articles related to use of hyperbaric oxygen (HBO) after radiation.

1Division of Laryngology, Department of Otolaryngology–Head and Neck Surgery, University of Washington School of Medicine, Seattle, Washington, USA
2Department of Otolaryngology–Head and Neck Surgery, Shin-Kong Wu-Ho-Su Memorial Hospital, Taipei, Taiwan

Corresponding Author:
Clint T. Allen, MD, Department of Otolaryngology–Head and Neck Surgery, University of Washington Medical Center, 1959 NE Pacific St, Box 356515, Seattle, WA 98195, USA.
Email: allencl@uw.edu

Received March 26, 2013; revised July 8, 2013; accepted August 13, 2013.
Discussion
Pathophysiology of Early and Late XRT-related Tissue Changes
In 1972, Lederman12 characterized post-XRT tissue changes as soft tissue edema, skin damage, perichondritis, and cartilage necrosis. Though useful as a clinical guide, this list does not completely convey the complex temporal nature or etiology of XRT-related changes to normal tissue. Early and late effects of ionizing XRT on normal tissue are differentiated both in their pathophysiology and clinical presentation. Early XRT-related changes are caused by death of replicating cells due to DNA damage either directly or via generation of reactive oxygen species.13 This damage and subsequent cell death leads to structural breakdown and general loss of function. Ciliated epithelium, blood vessels, and secretory glands appear especially sensitive to early XRT effects.14-16 These early changes result in edema, erythema, sloughed tissues, inspissated secretions, and possibly hemorrhage that manifest as dysphonia, dysphagia, pain, and potentially airway compromise. Recovery of tissues after the completion of treatment is expected, as loss of tissue progenitor cells is usually not observed in differentiated both in their pathophysiology and clinical presentation. Early XRT-related changes are caused by death of replicating cells due to DNA damage either directly or via generation of reactive oxygen species.13 This damage and subsequent cell death leads to structural breakdown and general loss of function. Ciliated epithelium, blood vessels, and secretory glands appear especially sensitive to early XRT effects.14-16 These early changes result in edema, erythema, sloughed tissues, inspissated secretions, and possibly hemorrhage that manifest as dysphonia, dysphagia, pain, and potentially airway compromise. Recovery of tissues after the completion of treatment is expected, as loss of tissue progenitor cells is usually not observed in different radiation models.13,17 Accordingly, most studies evaluating acute changes in vocal function during and after radiation therapy for laryngeal carcinoma demonstrate significant decline during radiation but significant improvement to near-baseline quality within months of completing therapy.18-22

Conversely, late XRT-related changes to normal tissue result from vascular damage and fibrosis. These changes are typically progressive and irreversible.10,15 Arterial vessels and the capillary microvasculature undergo changes that lead to endarteritis obliterans, ultimately causing ischemia and hypoxia of affected tissues.14,23 Capillary density loss of 60% to 80% occurs in irradiated tissue, which appears largely incapable of microvascular recovery, due to irreversible fibroblast and stromal damage.24 Patients may demonstrate progressive edema, muscle fibrosis, cricoarytenoid joint fixation, sloughing of tissue, perichondritis with eventual frank cartilage necrosis, and/or fistula formation,10,24 manifesting as vocal fold motion impairment, pain, need for tracheotomy, and/or significant dysphagia.25-28

Chondronecrosis occurs with loss of microvasculature and tissue ischemia and is one possible manifestation of late XRT-related tissue change. Cartilage itself has few blood vessels and rare proliferating cells, making it intrinsically resistant to the direct effects of ionizing radiation. In contrast, the perichondrium, from which the underlying cartilage receives its nutrient supply, is highly proliferative and quite sensitive to XRT.29 Chondronecrosis follows perichondritis and/or breakdown of the overlying mucosa.10,14 As laryngeal cartilages ossify with age, they develop their own blood supply and become susceptible to XRT damage. The arytenoid cartilages commonly ossify in adults and are a common site of chondronecrosis in the larynx, reinforcing this principle.30 Laryngeal edema observed with both early and late XRT-related changes results from increased vascular permeability in the setting of decreased lymphatic and vascular outflow.10,14,23 This is a distinct process from chondronecrosis, which occurs secondary to the loss of microvascular supply to the cartilage.10,24 Classification schemes by Chandler31 and the Radiation Therapy Oncology Group34 have been generated for research and clinical decision-making purposes (Table 1). These classifications group together the clinical manifestations of both early and late XRT-related tissue changes, including those distinct changes that lead to soft tissue edema or chondronecrosis. Signs and symptoms occurring less than 3 months after completion of XRT are termed early, whereas those occurring more than 3 months after XRT are late in these schemes. Further complicating the issue, there is great variability in the definition of radionecrosis in the literature, with the term often being used in manuscripts to refer to variable amounts of edema, frank necrosis, or both.10,32,33

The majority of patients with advanced LxSCC are treated with chemotherapy in addition to XRT, but it is unclear if this combination increases the risk of development of chondronecrosis. The improved locoregional control observed with CRT over XRT alone in patients with advanced epithelial malignancies is thought to occur in part through radiosensitization.34 While severe early and late XRT-related toxicity occurs more frequently in patients receiving CRT compared to XRT alone,34 no definitive increase in the rate of chondronecrosis development has been reported.

Intensity-modulated radiotherapy (IMRT)35 allows more focused radiation fields and preservation of laryngopharyngeal tissue outside of the primary tumor site. IMRT has led to reduced rates of osteoradionecrosis of the mandible in patients with oral cancer.36 Patients with high pharyngeal primary malignancies treated with IMRT demonstrate less posttreatment dysphagia when emphasis is placed on preserving the hypopharynx and larynx.37 Dysphagia remains a significant issue following IMRT of laryngeal malignancies, due to field inclusion of the larynx and the hypopharyngeal musculature.38 Reduced rates of laryngeal chondronecrosis development with IMRT compared to standard fractionated XRT with primary laryngeal tumors would be expected but has not yet been demonstrated in large-scale studies.

Differentiating Late XRT-related Tissue Changes and Tumor Recurrence
Nearly all patients experience some degree of early XRT-related tissue changes that typically resolve within 8 to 12 weeks of finishing treatment.10,13,17,31 The rate of development of late XRT-related tissue changes varies widely, likely due in part to the variable definitions used between...
studies. Laryngeal edema lasting 3 months or more is the most common late effect following XRT, occurring in up to 40% of patients receiving 70 cGy.24,39 The rate of edema persisting beyond 6 months after XRT drops sharply to 10% or less in most studies.40,41 Development of true chondronecrosis after XRT is low for early LxSCC with published rates of 1% to 2%23,30,41,42 but may be higher for advanced laryngeal tumors.30,43 Development of late XRT-related tissue change usually occurs within the first several years of completing XRT but can occur up to 50 years later.10,23 Dose and type of radiation, upper respiratory tract infection, continued tobacco and alcohol consumption, and laryngeal trauma all increase the risk of developing late XRT-related tissue changes.31,39,44

Table 1. Classifications of XRT-related tissue changes.

<table>
<thead>
<tr>
<th>Chandler</th>
<th>Radiation Therapy Oncology Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Symptoms may include: Slight hoarseness and mucosal dryness</td>
</tr>
<tr>
<td></td>
<td>Signs may include: Slight edema and presence of telangiectasias</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Symptoms may include: Moderate hoarseness and mucosal dryness</td>
</tr>
<tr>
<td></td>
<td>Signs may include: Moderate edema and erythema, some TVC hypomobility</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Symptoms may include: Severe hoarseness with dyspnea, moderate odynophagia and dysphagia</td>
</tr>
<tr>
<td></td>
<td>Signs may include: Marked edema, skin changes anterior neck, severely impaired or fixed unilateral TVC</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Symptoms may include: Respiratory distress, severe pain and odynophagia, weight loss, dehydration</td>
</tr>
<tr>
<td></td>
<td>Signs may include: Fistula, fetid odor, fever, severe skin changes anterior neck and laryngeal airway obstruction due to edema</td>
</tr>
</tbody>
</table>

Abbreviation: TVC, true vocal cord.

surgical specimens in the presence of late XRT-related tissue changes. Excluding 1 study that reported very low rates of late XRT sequelae and no recurrences following treatment of early glottic cancers,51 studies suggest that 46% to 71% of larynges demonstrating late XRT-related tissue changes harbor occult malignancy. Conversely, fewer than 25% of patients who develop recurrence have persistent late XRT-related tissue changes.30,52 Recurrent or persistent malignancy must be considered when evaluating patients with persistent, late XRT-related tissue changes.

**Measures of Laryngeal Tumor Recurrence**

**Biopsy.** Variable time points are used by clinicians, 2 to 3 months being common, to begin to consider the presence of persistent malignancy after definitive XRT treatment. When close clinical examination raises suspicion, directed biopsies of the larynx in the operating room to rule out residual/recurrent malignancy can be difficult,10,23,31 and there is concern among some authors that repeated biopsies of the irradiated larynx may itself induce perichondritis and chondronecrosis.10,11,32,44 Viani et al52 evaluated the role of operative biopsies when recurrence was suspected and found a high positive predictive value but a low negative predictive value (ie, a negative biopsy was poor at ruling out the presence of cancer in the larynx). In this series, 9 of 12 patients with exam findings concerning for disease recurrence but with negative operative biopsies were found to have recurrent cancer following surgical resection. The negative predictive value of biopsies is even lower when late XRT-related tissue changes are present.55,56
**Imaging.** The presence of gas bubbles, arytenoid sloughing, and cartilage fragmentation are suggestive of chondronecrosis on computed tomography (CT).57 Yet, CT and magnetic resonance imaging (MRI) are poor at differentiating between tissue fibrosis/necrosis and recurrent malignancy with high sensitivity for an abnormality but low specificity for either process.58-60 Great interest has been applied to the utility of positron emission tomography (PET) or combination PET/CT in differentiating these processes with several early studies suggesting superiority of PET over CT or clinical exam.61,62 A recent meta-analysis pooled 8 studies using PET to differentiate recurrent malignancy from late XRT-related tissue changes and demonstrated sensitivity of 89% and specificity of 74%.63 Interestingly, the same group investigated the ability of PET to screen for those patients who need operative biopsy and showed perfect sensitivity and negative-predictive value, implying that no patient with recurrent cancer would have been denied operative biopsy if the decision had been made based on the results of the PET alone.64 In these studies, PET/CT was generally performed when the clinical scenario dictated a need to differentiate between recurrence and radiation effects alone, as opposed to scheduled posttreatment surveillance imaging, so timing was variable (median time from completion of XRT to imaging was 8.7 months). PET or PET/CT performed less than 12 weeks following completion of XRT may be less accurate in differentiating persistent disease from late XRT-related tissue changes.55

While PET appears to hold promise as a screening tool, large-scale clinical trials would need to be performed to ensure high sensitivity. Figure 1 demonstrates examples of using PET/CT to differentiate recurrent malignancy from late XRT-related tissue changes alone.

**Other measures of recurrence.** Patients often demonstrate vocal fold mobility dysfunction at the time of LxSCC diagnosis. Failure of recovery of vocal fold motion after completion of XRT strongly predicts treatment failure.66 Presence of any of these clinical scenarios should alert the clinician to a heightened degree of vigilance during post-XRT surveillance.

### Treatment of XRT-related Tissue Changes

Classifications such as that proposed by Chandler31 (Table 1) have been used in the treatment decision-making process. Grade I and II XRT-related tissue changes can typically be managed with outpatient supportive care alone. Grade III reactions require more aggressive treatment, with therapy aimed at preventing infection and progression of laryngeal tissue damage. Many authors recommend hospitalization and treatment with humidified air, corticosteroids, antimicrobials, proton pump inhibitors, and airway management appropriate for the degree of obstruction. Grade IV reactions are severe, usually resulting in the need for tracheotomy in addition.

Treatment of severe XRT-related tissue changes with antimicrobials is common, with many authors advocating the use of culture directed antibiotics.67,68 Diverse bacterial profiles have been identified in samples of osteonecrosis, including robust speciation of anaerobic bacteria.69,70 Parallel studies have not been completed in patients with severe XRT-related tissue changes in the larynx. Biofilm formation may contribute to the chronicity of severe XRT-related tissue changes either directly or indirectly through secretion of pro-inflammatory mediators.71

**Hyperbaric oxygen.** Hyperbaric oxygen has been used to treat severe XRT-related tissue changes and is 1 of 13 indications approved as appropriate for treatment with HBO by the Undersea and Hyperbaric Medical Society.72 HBO treatment consists of delivering 100% oxygen in a pressurized chamber, effectively increasing the partial pressure of oxygen in tissues to promote wound healing.73,74 A review of the literature reveals 7 case series reporting outcomes of HBO to treat late XRT-related tissue changes in the larynx following treatment of head and neck cancer. Table 3

### Table 2. Studies evaluating tumor recurrence in the presence of late XRT-related tissue changes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor</th>
<th>N</th>
<th>Clinical definition of late XRT-related tissue change used in study</th>
<th>No. with late XRT-related tissue change (%)</th>
<th>No. with pathologically proven recurrence (% of patients with late XRT-related tissue change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kagan 1974</td>
<td>T1-T4 Larynx</td>
<td>n/a</td>
<td>Edema &gt; 6 mo.</td>
<td>41 (n/a)</td>
<td>19 (46%)</td>
</tr>
<tr>
<td>Ward 1975</td>
<td>T1-T4 Larynx</td>
<td>n/a</td>
<td>Edema &gt; 6 mo.</td>
<td>43 (n/a)</td>
<td>23 (53%)</td>
</tr>
<tr>
<td>Mills 1979</td>
<td>T1-T3 Larynx</td>
<td>96</td>
<td>Persistent edema</td>
<td>13 (14%)</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Mintz 1981</td>
<td>T1-T4 Larynx</td>
<td>348</td>
<td>Perichondritis</td>
<td>52 (15%)</td>
<td>26 (50%)</td>
</tr>
<tr>
<td>Fu 1982</td>
<td>T1-T4 Larynx</td>
<td>247</td>
<td>Edema &gt; 3 mo.</td>
<td>38 (15%)</td>
<td>17 (45%)</td>
</tr>
<tr>
<td>Flood 1984</td>
<td>T1-T4 Larynx</td>
<td>n/a</td>
<td>Edema and TVC fixation</td>
<td>8 (n/a)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Wiernik 1990</td>
<td>T1-T4 Larynx &amp; Hypopharynx</td>
<td>713</td>
<td>Persistent edema</td>
<td>14 (2%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Turner 1991</td>
<td>T1-T4 Larynx</td>
<td>141</td>
<td>Persistent edema</td>
<td>9 (6%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Stevens 1994</td>
<td>T1/T2 Larynx</td>
<td>145</td>
<td>Persistent edema</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Abbreviation: TVC, true vocal cord.
summarizes these studies and highlights the quite favorable functional outcomes documented, with many suggesting high rates of avoidance of total laryngectomy (TL), fistula closure, and eventual tracheotomy decannulation.

Analysis of these studies reveals their strengths and weaknesses. Patients included in these studies received variable doses of XRT (4500-7500 Gy) for primary tumors at multiple head and neck sites (oral cavity, oropharynx, hypopharynx, and larynx). Further, studies vary on the specifics of the HBO technique, including number of treatments (3-80), duration (1-2 hours) and pressurization (2.0-2.5 ATM) of each treatment. These details highlight the lack of standardization of HBO treatment for late XRT-related tissue changes and the paucity of quality data supporting its use. As HBO therapies become more available, large-scale, prospective, and ideally randomized trials are needed to indeed determine if HBO can be considered a standard-of-care treatment for late XRT-related tissue changes in the larynx.

In addition to evaluating structural larynx preservation, decannulation, and enteral feeding tube independence, future studies must use validated outcomes tools to study the effects of HBO on voice and swallowing quality of life, such as the Voice Related Quality of Life and the Eating Assessment Tool (EAT-10).

A common concern regarding the use of HBO is its potential tumor-promoting properties. In vitro and in vivo analysis reveals no tumor growth or proliferation-promoting effects of HBO, and examination of the existing clinical literature fails to support a cancer-causing or growth-enhancing effect by HBO. Interestingly, locoregional control of head and neck squamous cell carcinoma (HNSCC) improves when HBO is added to XRT; however, use of HBO during XRT has largely been abandoned due to no measurable positive effect on disease-specific survival and the cumbersome logistics of performing XRT and HBO together.

Surgery. Persistent malignancy and disease recurrence are absolute indications for salvage surgical intervention. While TL is indicated for many patients after XRT failure, carefully selected patients may be candidates for salvage partial laryngectomy (SPL). Both open and endoscopic, laser-assisted SPL have oncologic outcomes equal to that of salvage TL following XRT failure for early glottic and selected supraglottic malignancies. Whether a SPL is appropriate depends on the overall clinical condition of the patient as well as the original T-stage. Others have advocated surgical debridement of necrotic tissue with soft tissue coverage of the defect as needed. Comfort levels with these “non-TL” approaches at laryngeal preservation following XRT are highly institution and clinician dependent.

Management of the cancer-free but dysfunctional larynx after XRT that does not respond to conservative treatment is less clear, particularly if there is pain. Following XRT for LxSCC, 20% to 40% will develop variable degrees of laryngopharyngeal dysfunction with a subset of patients requiring a long-term or permanent surgical airway. Patients dissatisfied with a permanent tracheotomy and/or enteral feeding may be best served by surgical intervention to provide a definitive, permanent surgical airway or to achieve aspiration-free swallow function. The majority...
of these patients undergo TL. Laryngotracheal separation/diversion procedures are available and can be used with success in patients with chronic aspiration, but reports evaluating efficacy and complications rates in patients with severe late-XRT tissue changes are lacking. Patients who undergo TL for laryngopharyngeal dysfunction demonstrate good postoperative swallow function with only rare needs for continued enteral nutrition support. Yet, complication rates associated with salvage TL after XRT are not insignificant, with roughly one quarter of patients developing a pharyngocutaneous fistula.

**Implications for Practice**

McGuirt et al have proposed a suggested treatment algorithm for patients with late XRT-related tissue changes following organ preservation therapies. Care must be taken when following a standardized protocol: Defining what constitutes a dysfunctional larynx and subsequently when therapeutic intervention is indicated for a cancer-free patient may be difficult but necessary before a universal algorithm can be generated.

The high rate of occult cancer being present in larynges that demonstrate late XRT-related tissue changes despite negative biopsies must always be considered and included in patient counseling. The most current evidence suggests that PET, when compared to CT or MRI, may be more useful to screen for patients who require operative biopsies. Once the clinician feels comfortable that malignancy is not present, based on imaging and perhaps negative biopsies, a number of surgical and nonsurgical options are available to try and salvage the cancer-free but dysfunctional larynx. Prospective research with standardized protocols is needed to determine if HBO therapy can be considered a standard-of-care treatment option for the dysfunctional, irradiated larynx. If needed, salvage TL carries the risk of postoperative complications but usually results in definitive airway control and aspiration-free swallow.

**Author Contributions**

Clint T. Allen, conception of study, drafting of article, final approval; Chia-Jung Lee, design of study, revision of article, final approval; Albert L. Merati, design of study, revision of article, final approval.

**Disclosures**

**Competing interests:** None.

**Sponsorships:** None.

**Funding source:** None.

---

**Table 3. Summary of case series evaluating efficacy of hyperbaric oxygen (HBO) treatment for late radiation therapy (XRT)-related tissue changes.**

<table>
<thead>
<tr>
<th>Article (first author)</th>
<th>Timeframe</th>
<th>N</th>
<th>Chandler Class</th>
<th>Time from XRT to Symptoms</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart 1976⁷⁵</td>
<td>1969-1975</td>
<td>5</td>
<td>IV</td>
<td>Not reported</td>
<td>1/5 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/5 fistulae closed with HBO alone</td>
</tr>
<tr>
<td>Ferguson 1987¹⁵</td>
<td>1979-1985</td>
<td>8</td>
<td>III, IV</td>
<td>3-15 mos</td>
<td>1/9 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/1 fistulae closed with HBO alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/3 patients with tracheotomy were decannulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7/8 with resolution of pre-HBO pain</td>
</tr>
<tr>
<td>Feldmeier 1993⁷⁶</td>
<td>1980-1985</td>
<td>9</td>
<td>III, IV</td>
<td>3 mos-2 yrs</td>
<td>0/9 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/4 fistulae closed with HBO alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/3 patients with tracheotomy were decannulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7/9 had usable voice after HBO</td>
</tr>
<tr>
<td>London 1998⁷⁷</td>
<td>1995-1998</td>
<td>5</td>
<td>III, IV</td>
<td>Not reported</td>
<td>0/5 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/4 patients with tracheotomy were decannulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5/5 patients had moderate to significant improvements is symptoms</td>
</tr>
<tr>
<td>Filintsis 2000²⁴</td>
<td>1990-1996</td>
<td>18</td>
<td>III, IV</td>
<td>3 mos-30 yrs</td>
<td>5/18 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4/13 patients with tracheotomy were decannulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13/18 had major improvements in symptoms</td>
</tr>
<tr>
<td>Narozny 2005⁷⁸</td>
<td>1998-2002</td>
<td>6</td>
<td>III, IV</td>
<td>2-22 mos</td>
<td>0/6 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/1 fistulae closed with HBO alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/3 patients with tracheotomy were decannulated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/6 had major improvements in symptoms</td>
</tr>
<tr>
<td>Roh 2009⁶⁷</td>
<td>2002-2007</td>
<td>6</td>
<td>IV</td>
<td>4-16 mos</td>
<td>1/6 required total laryngectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5/6 had improvements in symptoms</td>
</tr>
</tbody>
</table>
References


