

Contemporary Management of Advanced Laryngeal Cancer

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ABSTRACT: The treatment of advanced laryngeal cancer has undergone a paradigm shift in recent years, with an increase in chemoradiation for organ preservation and a decrease in primary surgery. This review will summarize the contemporary management of advanced laryngeal cancer and discuss treatment-related toxicity and strategies to improve outcomes.

Key Words: Larynx neoplasms, squamous cell cancer, Speech-language pathology, treatment, surgery, radiation, chemotherapy, survival, outcomes, swallowing.

Level of Evidence: NA.

The treatment of advanced laryngeal cancer has evolved in the past 2 decades, with an increase in the use of nonoperative treatment for organ preservation and a decrease in the use of primary surgery. This paradigm shift dates to the Veteran's Affairs (VA) Laryngeal Cancer Study, published in 1991, which showed high rates of laryngeal preservation in advanced laryngeal cancer using chemoradiation, without a reported decrement in survival.¹ The induction chemoradiation regimen described in the VA trial has largely been replaced by concurrent chemoradiation regimens based on the subsequent Radiation Therapy Oncology Group (RTOG) Trial 91-11, which demonstrated improved locoregional control rates with concurrent therapy.² These data have led to enthusiasm for the use of organ preservation regimens, reflected by an increase in the use of chemoradiation in both community and academic settings, and a corresponding decrease in the use of primary surgery.³⁻¹⁰

The favorable outcomes of organ preservation for advanced laryngeal cancer may not apply outside of clinical trial settings, suggesting this approach may not be suitable for all patients. Both National Cancer Data Base (NCDB) and Surveillance, Epidemiology, and End Results (SEER) registry data have demonstrated a decrease in survival in patients with laryngeal cancer, in parallel with an increase in the use of nonoperative treatment that is not due to an increase in the incidence

of advanced stage disease.^{3,11} Patients with T4 tumors have been shown to have worse organ preservation rates and poorer survival with nonoperative treatment. In the VA laryngeal cancer study, salvage laryngectomy was performed in 56% of patients with T4 disease, compared to 29% for T1-T3 disease.¹ Patients with T4 disease comprised 26% of patients in the VA trial and were largely excluded from RTOG 91-11, with low-volume T4 disease, exclusive of cartilage involvement or significant tongue base extension, comprising 10% of that study population. The RTOG 91-11 study found an approximately 10% decrement in survival when salvage laryngectomy was required compared to those who did not.¹²

A large single institution study of nearly 500 patients with laryngeal cancer demonstrated that patients with stage IV disease had worse survival with organ preservation, compared to primary surgical treatment.¹³ Survival was equivalent for stage I-III disease treated surgically or with chemoradiation. Patients with T4 lesions had worse survival with chemoradiation (25%) compared to primary surgery (55%). NCDB data demonstrates that chemoradiation is associated with an increased risk of death for patients with stage IV disease.¹⁴ Taken together, these data suggest that patients with very advanced primary tumors are unsuitable for organ preservation. While causation cannot be proven in retrospective studies, temporal trends suggest that the broad application of clinical trial data may be responsible for poorer outcomes outside of the clinical trial setting, where careful attention is paid to selection of patients best suited for organ preservation strategies.

The poorer outcomes associated with chemoradiation may be due to selection bias, with sicker patients treated nonoperatively, or to non-cancer-related mortality. A metanalysis of 3 RTOG trials by Machtay et al¹⁵ demonstrated that severe late toxicity, defined as grade 3 or higher toxicity related to laryngopharyngeal dysfunction, feeding tube dependence >2 years after treatment, and non-cancer related death suspected to be due to laryngeal dysfunction, occurs in 43% of patients. Enrollment in these trials required acceptable performance status, and patients with evidence of severe pretreatment laryngeal

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dysfunction were excluded from this meta-analysis, which suggests that the true incidence of severe late toxicity may in fact be greater when strict clinical trial criteria are not applied to selection of patients for organ preservation. A 10-year follow-up report of RTOG 91-11 patients found an increase in non-cancer-related deaths in patients treated with chemoradiation at 10 years, suggesting that improved laryngeal preservation rates with concurrent regimens may adversely impact survival due to severe late toxicity.¹⁶

A retrospective review of patients with laryngeal cancer using SEER-Medicare data demonstrated that chemoradiation was 4-fold more likely to be used in patients with advanced laryngeal cancer; however, survival was significantly better in patients treated with surgery and postoperative radiation.¹⁷ In this same cohort, pretreatment dysphagia, treatment with chemoradiation, and salvage surgery were significant predictors of an increased risk of long-term dysphagia, weight loss, gastrostomy, and tracheostomy dependence.¹⁸ Initial treatment with surgery and postoperative radiation were associated with a lower odds of late pneumonia. These late toxicities were associated with poorer survival, with the greatest risk of death at 5 years associated with pneumonia.

Using a set of quality indicators based on NCCN guidelines for larynx cancer care, higher-quality care, measured by greater guideline compliance, was associated with improved survival regardless of treatment modality.¹⁹ However, even after controlling for quality, there remained a survival advantage for primary surgery with postoperative radiotherapy in elderly patients. Quality was associated with outcomes, with higher-quality care associated with a lower odds of long-term weight loss, tracheostomy or gastrostomy dependence, and pneumonia, but no impact on the odds of late dysphagia.²⁰ However, higher-quality care was associated with a lower risk of death in patients with dysphagia, weight loss, tracheostomy, and pneumonia, but was not associated with differences in survival in patients with gastrostomy dependence.

These data suggest that dysphagia is common following laryngeal cancer treatment, but that higher-quality care process measures are associated with a reduction in the incidence of late toxicities related to airway and swallowing impairment, and reduced mortality when these toxicities occur. An important exception was late mortality associated with gastrostomy dependence: while higher-quality care was associated with a reduced incidence of gastrostomy dependence, it was not associated with significant differences in survival in patients with long-term gastrostomy dependence. Such patients may be beyond the reach of successful intervention. Severe dysphagia associated with nil per os (NPO) status has been shown by others to be associated with a significantly increased risk of death, emphasizing the poor prognosis associated with progression to this point.²¹

Strategies to avoid late gastrostomy dependence include patient selection, avoidance of prophylactic gastrostomy, targeted radiation dosimetry to limit toxicity to the constrictor musculature, and aggressive therapeutic interventions during and after treatment. Patients

with pretreatment dysfunction are known to be at increased risk for late toxicity with organ preservation strategies, because preservation of an organ that is not functional does not result in restoration of function, and function may actually worsen due to the effects of treatment. Radiation doses of ≥ 60 Gy to the constrictor musculature have been shown to be associated with an increased risk of severe late toxicity and long-term gastrostomy use in the RTOG meta-analysis and a number of institutional studies.²²⁻²⁵ These effects are due to muscle injury and increase the risk of aspiration in a dose and volume-dependent manner.²⁵

Prolonged NPO status is associated with poorer long-term swallowing outcomes and an increased risk of long-term gastrostomy dependence.^{21,26-32} There is substantial evidence that prophylactic gastrostomy placement, intended to facilitate weight maintenance and enteral feeding during treatment, is associated with worse long-term swallowing outcomes because of decreased use of the swallowing musculature, which is associated with muscle atrophy and an increased incidence of late dysfunction.^{33,34} The prophylactic use of swallowing exercises that actively engage these muscles during radiation is associated with maintenance of muscle function and quality by maintaining muscle bulk and preservation of a near-normal diet.^{33,34} This is facilitated by avoiding routine gastrostomy placement and the active engagement of speech-language pathologists (SLP) in laryngeal cancer care.

SLP involvement has been shown to favorably impact swallowing outcomes. Swallowing exercises instituted before, during, and after the onset of radiation have been shown to be associated with improved post-treatment swallowing function and quality of life.³⁵⁻³⁹ In randomized controlled trials of SLP-directed swallow therapy, radiated patients who perform swallowing exercises are four-fold more likely to return to a regular diet and have improved subjective and objective post-treatment swallowing function.^{33,40,41} The active participation of SLP in swallowing therapy is associated with improved compliance with exercises and greater work done.³³ However, SLP care is not uniform, with variability in their employment among differing practice settings and variation in practices.^{42,43} In SEER-Medicare laryngeal cancer patients, SLP care appears underutilized and largely limited to patients undergoing total laryngectomy, or those in whom swallowing dysfunction is already present, but is associated with a reduced likelihood of dysphagia, weight loss, and pneumonia, and most significantly, with a reduced risk of death.⁴⁴ These data suggest that SLP care should be a routine part of the management of laryngeal cancer patients to reduce the incidence and impact of severe late toxicity.

There are well-recognized limitations when comparing different treatment modalities using retrospective data, and randomized trials are the gold standard for detecting differences in outcomes while minimizing bias. The VA laryngeal cancer study remains the only randomized controlled trial with a surgical arm, 16 years after its publication, and it is unlikely that randomized controlled trials with a surgical arm will be performed

in the future given patient and clinician biases and preferences. Chemoradiation has become an accepted standard of care of advanced laryngeal cancer. These data emphasize the significance of treatment-related toxicity, the importance of recognizing high-risk patients, a recognition of the continued role of surgery in this population, and the need to incorporate strategies aimed at reducing treatment-related sequela in current and future efforts at optimizing outcomes in this population.

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